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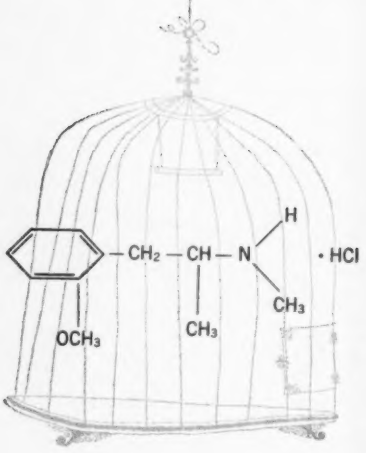

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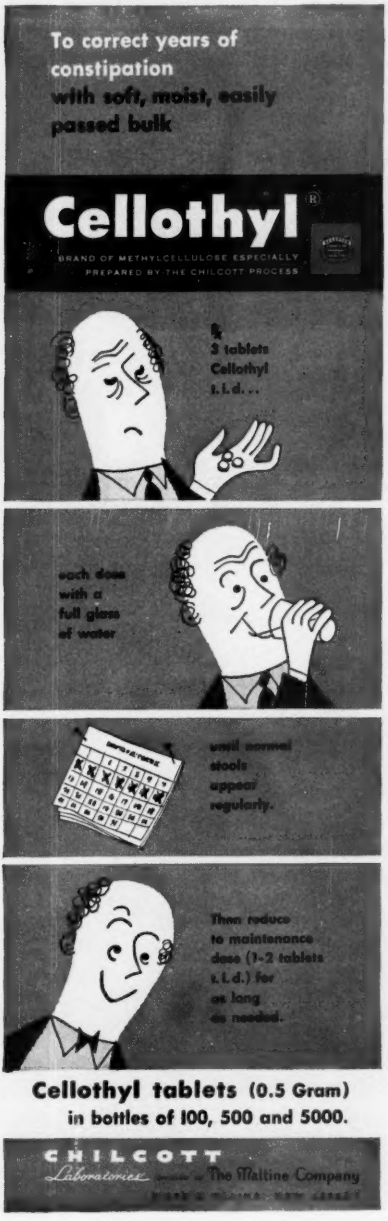
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1. Newey, J. A., and Goetzl, F. R.: Permanente Med. Bull. 7:67 (July) 1949.

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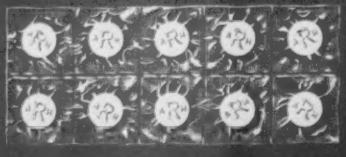

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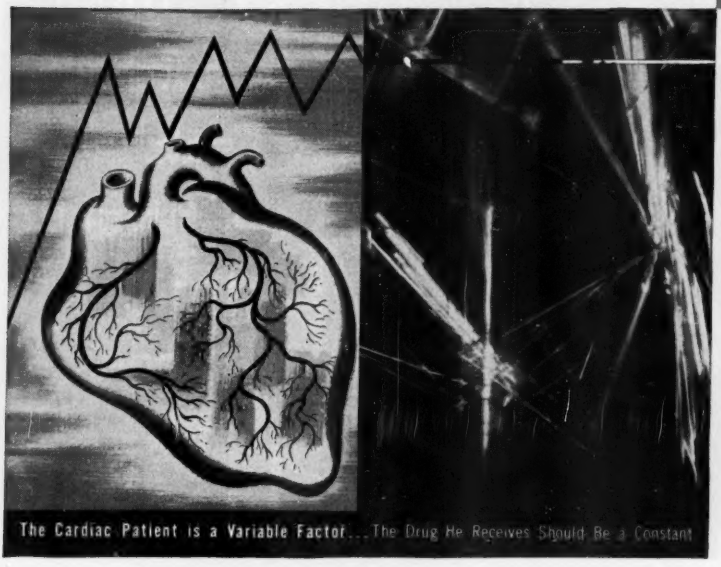

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Volume 245 JULY 5, 1951 Number 1

DIABETIC ACIDOSIS*

Results of Treatment in 67 Consecutive Cases

REED HARWOOD, M.D.†

BOSTON

A REVIEW of the results of treatment of diabetic coma on the Medical Service at the Massachusetts General Hospital in the pre-insulin era shows that the mortality rate was close to 100 per cent. In the period from January, 1942, to November, 1944, there was a mortality of 20 per cent in a series of 35 severe and moderately severe cases of diabetic acidosis. This drop in mortality in the twenty years following the discovery of insulin represents a tremendous improvement. However, such a mortality in any acute illness constitutes a serious challenge. At that time we had tended to accept this death rate as the best we could do with the type of patient and the conditions of work that are to be found in a large general hospital. This acceptance was in part justified by the figures published from other similar clinics as shown in Table 1.

The low mortality rate at the New England Deaconess Hospital was discounted as being due to a type of patient more favorable for treatment, and to a permanent staff with more experience in this special field than might be found in a general hospital. Late in 1944, however, under some chiding from Dr. Joslin and his associates, we determined to make an all-out effort at the Massachusetts General Hospital to reduce our death rate in diabetic acidosis. This new effort included more aggressive treatment on the part of the house staff, more active consultation with the visiting staff and laboratory service (hitherto lacking at night and on holidays) whenever needed. The prompt improvement in our results can be attributed in part to each of these changes, but the greatest share of the credit goes to the interns and residents whose zeal and skill made this record possible. This paper reports our success in 67 consecutive cases admitted to the medical wards of the Massachusetts General Hospital between November 1, 1944, and June 1, 1950. The single fatality was the thirteenth case in this series, a 75-year old woman who died in July, 1945. Since that time, 54 consecutive patients have survived.‡

TABLE 1. *Deaths in Diabetic Acidosis.*

HOSPITAL	PATIENTS TREATED	PERCENTAGE OF DEATHS
Mayo Clinic[1]	108	7.4
Los Angeles County General Hospital[2]	315	33.3
Philadelphia General Hospital[3]	268	43.7
Detroit Receiving Hospital[4]	28	28.5
New England Deaconess Hospital[5]	126	2.4*
Montreal General Hospital[6]	125	26.4
New York Hospital[7]	71	11.0

*The New England Deaconess Hospital recently recorded 92 cases with no death.[8]

MATERIAL

This series includes all the severe and moderately severe cases of diabetic acidosis treated over a period of five and a half years, except for those patients admitted to the Pediatric Service and to the private floors. Mild cases of acidosis were excluded; in the series all but 6 patients had a serum carbon dioxide content of less than 10 milliequiv. per liter. Fifty-seven patients accounted for the 67 admissions. Eight patients were admitted twice in diabetic acidosis and one patient had three admissions. There were 28 males and 29 females. The average age was 36 years. The youngest was 14; the oldest was 75. In tabulating the data (Tables 2, 3 and 4) it was found convenient to divide the cases into three groups according to a rough estimate of the severity of each case. Group A contains the severe cases, Group C the moderate ones. Group B includes those patients who in our experience had acidosis of "average" severity.

CLINICAL DATA

Precipitating factors. An attempt was made in each case to determine the factors that led to aci-

*From the Medical Service, Massachusetts General Hospital.

†Chief, Diabetes Clinic, and assistant physician, Massachusetts General Hospital.

‡Since this paper was prepared for publication, there have been 8 additional cases. One of these died, of potassium deficiency and peritonitis.[9]

dosis. The most frequent cause was infection. Long-continued neglect of the diabetic regimen was found almost as frequently. One third of the patients had neglected to take their insulin for a period of one to three days prior to admission. One half of the patients appeared to have developed diabetic acidosis as a result of a combination of two or three of these factors. There were 13 patients whose diabetes had not previously been diagnosed or treated. In 4 cases the cause of diabetic acidosis was not determined.

Condition on arrival. The record in each case contains a brief description of the mental state of the patient on arrival. This is summarized in Table 6.

The term "semicomatose" is used to describe the state in which the patient is able to respond only to painful stimuli. In this series only one patient was completely unconscious on arrival, but several others lapsed into coma soon afterward. It is interesting to note that although 76 per cent of the patients in this series were considered critically ill on arrival only 34 per cent had a marked depression of the level of consciousness.

The blood pressure was determined in each case on admission. Most of the patients had diastolic pressures ranging from 60 to 85 mm. of mercury; thirteen had diastolic pressures under 60 mm., and in one of these the blood pressure could not be obtained.

It has been repeatedly pointed out[2, 3] that among the factors contributing to death in diabetic acidosis the depth of coma and the depression of the blood pressure are most important. It should be emphasized, however, that deaths from diabetic acidosis can occur in the absence of coma and shock; in fact, several of our acidosis deaths prior to 1944 occurred in patients whose condition on admission to the hospital was not at all alarming[10] (Table 7).

Laboratory Data

Blood sugar. Determinations of the blood sugar were made every one to three hours during the first twenty-four hours of treatment. The highest initial blood sugar was 1280 mg. per 100 cc., and the average for the entire group was 597 mg. The average for the 21 patients in Group A was 829 mg.

As a rule, the blood sugar fell quite steadily after the first two hours of treatment, reaching normal or near-normal levels in twelve to eighteen hours. In a number of the severest cases the blood sugar remained above 800 mg. for twelve hours or longer, despite large doses of insulin. In the few instances in which considerable quantities of dextrose were administered early in the treatment the blood sugar rose at first and declined more slowly than it did in patients who received little dextrose. This observation confirms a recent report by Franks and his co-workers.[4]

Serum carbon-dioxide content. This was determined on admission, and at one- to six-hour intervals during the first twenty-four hours of treatment. The average carbon-dioxide level for the series was 7.2 milliequiv. per liter. The highest was 12.3 and the lowest was 3.7. Although in the 21 severest cases the average was slightly lower (6.7 milliequiv. per liter), the carbon-dioxide level was not a reliable guide to the severity of the patients' illness, as Collen[2] has pointed out. In the present series the carbon-dioxide level began to rise quite regularly

Table 2. *Group A: Severe Acidosis.*

Case No.	Patient	Age	Mental State	Complications	Admission Blood Sugar	Admission Blood Carbon-Dioxide Content	Total Insulin Dosage
					mg./100 cc.	*milliequiv./liter*	*units*
1	J. O'B.	48	Drowsy	Gastroenteritis	800	8.3	1250
2	R. C.	44	Very drowsy		688	6.2	1475
3	C. D.	34	Semicomatose	Pneumonia gastroenteritis	1240	3.8	3620
4	M. M.	52	Drowsy		572	6.2	975
5	M. D.	26	Drowsy		628	7.2	1109
6	T. C.	30	Drowsy		800	10.4	1730
7	K. H.*	75	Semicomatose	Pyelonephritis	466	7.4	1150
8	C. D. F.	27	Very drowsy		783	6.2	3210
9	M. Y.	51	Very drowsy		768	6.0	2300
10	R. C.	44	Drowsy		922	6.0	2075
11	M. McK.	53	Very drowsy		1108	7.4	2580
12	J. K.	15	Semicomatose		890	9.2	6600
13	E. D.	57	Semicomatose		1048	5.8	5325
14	J. C.	68	Very drowsy	Myocardial infarction	1280	8.9	3220
15	L. LaS.	24	Semicomatose	Upper-respiratory infection	1015	4.2	3300
16	R. E.	42	Very drowsy	Perforated gastric ulcer	600	6.8	1350
17	R. P.	33	Semicomatose	Gastroenteritis Pharyngitis	872	3.7	1650
18	M. M.	17	Semicomatose	Pharyngitis	585	4.4	2025
19	F. G.	74	Comatose	Insulin resistance	460	9.1	17,000
20	E. LaV.	16	Very drowsy		860	6.8	3560
21	F. G.	74	Semicomatose	Insulin resistance	1031	8.3	10,500
Averages ...		39			829	6.7	2552†

*Died.
†Cases 19 and 21 not included in average.

during the first two or three hours of treatment, reaching levels of 18 to 27 milliequiv. per liter in five to twenty hours. In 2 cases values above normal (36 and 41 milliequiv. per liter, respectively) were obtained at the end of the twenty-four-hour period. One of these patients had received intravenously 52.5 gm. of sodium bicarbonate, an unusually large amount.

Blood nonprotein nitrogen. This was determined in 51 cases and was above 40 mg. per 100 cc. in 32 cases. In 15 of the 21 severest cases, the nonprotein nitrogen was over 60 mg. In all but 2 cases it had returned to normal in twenty-four hours.

Serum sodium, chloride, potassium and inorganic phosphorus. Determinations of these blood constituents were made on a number of the patients and are summarized in Table 8. The serum sodium and chloride tended to be distinctly below normal. The serum potassium and phosphorus tended to be above normal on admission and to fall to subnormal levels during the first few hours of treatment. These findings are in agreement with those of other observers.[11, 12]

TABLE 3. *Group B: Acidosis of Average Severity.*

CASE NO.	PATIENT	AGE	MENTAL STATE	COMPLICATIONS	ADMISSION BLOOD SUGAR	ADMISSION BLOOD CARBON-DIOXIDE CONTENT	TOTAL INSULIN DOSAGE
					mg./100 cc.	*milliequiv./liter*	*units*
22	M. S.	16	Conscious	Respiratory infection	400	8.7	313
23	R. C.	14	Conscious		404	7.8	560
24	S. L.	25	Conscious	Pyelonephritis Perinephric abscess	430	9.8	850
25	M. S.	26	Conscious		416	8.6	590
26	J. V.	18	Semicomatose	Carbuncle	364	5.2	605
27	F. L.	24	Conscious	Respiratory infection	380	6.3	1025
28	J. O'B.	48	Drowsy	Respiratory infection	400	12.3	504
29	J. G.	23	Conscious	Gastroenteritis	512	6.9	761
30	S. C.	18	Drowsy		392	9.9	555
31	G. S.	67	Drowsy	Myocardial infarction	740	11.8	555
32	J. O'B.	49	Very drowsy	Respiratory infection	690	10.7	516
33	A. S.	51	Semicomatose		380	4.8	668
34	F. P.	20	Conscious	Respiratory infection	394	8.2	620
35	E. H.	42	Conscious	Pneumonia	616	4.9	1120
36	E. M.	22	Drowsy	Otitis	600	4.5	1000
37	R. F.	44	Conscious	Abscess of arm	576	9.6	635
38	E. G.	40	Very drowsy	Pneumonia	468	6.4	1630
39	A. L.	56	Very drowsy	Myocardial infarction	496	5.1	1080
40	J. B.	18	Drowsy	Respiratory infection	565	7.1	850
41	S. S.	58	Drowsy		435	8.5	785
42	M. McK.	55	Conscious	Duodenal ulcer	500	7.4	750
43	E. B.	62	Drowsy	Congestive failure	526	5.9	690
44	B. C.	68	Drowsy	Gastroenteritis	885	9.7	1720
45	F. A.	22	Drowsy		520	5.4	1250
46	M. D.	28	Drowsy		685		500
47	J. B.	19	Drowsy	Respiratory infection	354	9.5	800
48	H. M.	19	Drowsy		442	5.8	1295
49	C. B.	15	Drowsy	Respiratory infection	386	7.1	870
50	F. F.	58	Drowsy	Respiratory infection	430	10.8	550
51	R. P.	34	Very drowsy	Pyelonephritis	745	3.7	1500
Averages ...		34.6			504	7.6	839

TREATMENT

General measures. Each case of diabetic acidosis was treated as an acute medical emergency. A house officer remained in constant attendance during the first twenty-four hours of treatment or until the patient's condition warranted routine ward care. A medical resident also took an active part in the management of treatment. The staff physician was called to see each case, and the author saw approximately half the cases. A laboratory technician was kept on duty for blood chemical determinations until the patient was considered out of danger.

As soon as the diagnosis of diabetic acidosis was made, the patient was started on insulin and intravenously administered fluids, as described below. A history was obtained when possible, and a careful physical examination was made in a search for infection, surgical emergencies and other complications. Blood was drawn at once for various chemical determinations. When it seemed advisable, an indwelling Foley catheter was placed in the bladder. A gastric lavage was performed when it was indicated by vomiting, nausea or inability to take fluids by mouth. Digitalis and various stimulants were employed in a limited number of patients. Penicillin came to be used routinely.

A treatment record, called a "Coma Sheet" was pinned to the wall by the bedside. At half-hourly or hourly intervals there were recorded on this sheet the patient's blood pressure, pulse, respiration and mental state; the amount and type of fluid given intravenously; the amount and type of fluid taken by mouth; the urinary output and the fluid lost by vomiting or lavage; the result of tests for urinary sugar and acetone; the dosage of insulin and other medications; and the pertinent reports from the chemistry laboratory. In this way a fairly complete chronologic account of the treatment and the prog-

ress of the patient was readily available for review and consultation.

Insulin. The initial dose of insulin, given as soon as the diagnosis was established, ranged from 50 to 200 units, depending on the seriousness of the case. The second dose was usually delayed until the report of the first blood sugar had been received. Thereafter insulin was given every half hour or hour, depending on the case and the response of the blood sugar. When a large dose was given half of it was usually given intravenously. In the more severe cases, doses of 100 to 200 units were given every half hour until the blood sugar had made a satisfactory response. The dosage was then reduced and the interval between doses lengthened, administration usually being stopped altogether when the blood sugar had fallen to 200 mg. per 100 cc. Thereafter insulin was administered every two to four hours according to the degree of glycosuria. Most of the patients in this series received large doses of insulin. The average total dose in the first twenty-four hours for the series was 1280 units. (This average does not include Case 19, reported below, who received 17,000 units in one day and on another occasion 10,500 units.)

A review of the literature indicates that in recent years some other hospitals have tended to use similar large doses of insulin. Joslin[5] reported a series of 126 cases in 1946 in which an average dose of only 282 units was given in the first twenty-four hours. However, his associate, Root,[13] in 1945 advocated considerably larger doses. Franks and others[4] gave an average dose of 930 units to a series of 28 patients. Lee and his co-workers,[14] treating a series of 28 comatose patients, gave an average dose of 723 units to the 22 patients who survived. Sheppard[15] reports a case in which 56,000 units of insulin was given in twenty hours. At the Massachusetts General Hospital, a review of the 35 cases treated there from 1942 to 1944 showed that the average dose of insulin was 518 units in the first twenty-four hours. The mortality in that series was 20 per cent. Our present practice had its beginnings in a suspicion that some of these patients had died because we had failed to administer sufficient amounts of insulin. As the present series grew, it was found that patients could safely tolerate the larger doses, and with this experience the practice became established. Only 8 patients developed hypoglycemia as a result of this treatment; in all but one instance (Case 21, reported below) the hypoglycemia was easily controlled by intravenous administration of dextrose.

Several comments on this treatment seem justified. In the first place, it is highly probable that many of these patients would have recovered if considerably smaller doses of insulin had been given. Whether some of the severest cases would have survived on the regimen recommended by Almy and others[7] (25 units every half hour until the urine is free of sugar and acetone) is questionable.

TABLE 4. *Group C: Moderate Acidosis.*

CASE NO.	PATIENT	AGE	MENTAL STATE	COMPLICATIONS	ADMISSION BLOOD SUGAR	ADMISSION BLOOD CARBON-DIOXIDE CONTENT	TOTAL INSULIN DOSAGE
					mg./100 cc.	*milliequiv./liter*	*units*
52	H. M.	45	Conscious	Cystitis	672	10.3	480
53	F. F.	53	Conscious	Furunculosis	276	7.3	175
54	J. P.	21	Conscious		424	8.4	390
55	E. O.	37	Conscious		483	5.8	604
56	A. D.	40	Drowsy	Pyelonephritis	382	8.5	365
57	F. B.	18	Drowsy	Respiratory infection	254	5.3	315
58	A. E.	49	Drowsy	Abscess, chest wall	360	9.0	450
59	P. P.	47	Drowsy	Pyelonephritis	412	7.0	330
60	D. M.	23	Drowsy		490	9.1	1400
61	S. M.	35	Conscious		445	7.2	578
62	M. McC.	47	Drowsy		640	5.2	1183
63	H. M.	52	Drowsy		544	9.6	400
64	A. P.	18	Very drowsy		545	8.0	685
65	F. B.	20	Drowsy	Respiratory infection	410	7.0	700
66	P. Z.	17	Drowsy	Abscess, buttock	484	7.2	695
67	J. D.	19	Drowsy		650	8.5	775
Averages		33.8			466	7.7	595

TABLE 5. *Precipitating Factors.*

	NO. OF CASES
Infection	30
Neglect of diabetes	29
Omitted insulin	20
Previously untreated diabetes	13
Cause not determined	4
Miscellaneous	
Myocardial infarction	2
Alcoholic excess	3
Duodenal ulcer	1
Perforated gastric ulcer	1
Head injury	1
Insulin resistance	2

It has been repeatedly emphasized that diabetic acidosis is a state of acute insulin deficiency, in which resistance to the effects of insulin grows as its administration is delayed. It seems logical, therefore, to give ample doses of insulin promptly and

frequently. It must be emphasized that such large amounts of insulin can be given safely only if the blood-sugar level is carefully followed. Yannet,[16] studying hypoglycemia in cats, found that large doses of insulin produced widespread cerebral damage, whereas a much smaller dose of insulin could cause equally severe hypoglycemia without producing the cerebral lesions.

TABLE 6. *Mental State on Arrival.*

	No. of Cases	Percentage
Conscious	15	22.3
Drowsy	29	43.2
Very drowsy	12	17.9
Semicomatose	10	14.9
Comatose	1	1.5

Intravenously administered fluids. All the patients in this series received fluids by the intravenous route. An account of the parenteral therapy may be divided into two groups, as our policy in regard to it changed considerably during the five-and-a-half-year period covered by this series. Most of the patients treated in the first three years (41 cases) were given at the start of treatment a mixture of normal saline solution with either sodium lactate or sodium bicarbonate; this was followed, when the blood sugar had made a satisfactory response, by either dextrose in saline solution or dextrose in water. In most instances the saline and lactate were given in the following proportions: 0.85 per cent solution of sodium chloride, 1500 cc.; molar sodium lactate, 80 cc. This solution, it should be pointed out, is strongly hypertonic to the sodium and chloride of the serum; in the amounts shown above the concentrations are: sodium, 188 and chloride, 138 milliequiv. per liter.

The amount of normal saline solution given ranged from 2 to 10 liters, the average in this earlier group being nearly 4 liters. The amount of sodium lactate ranged from 4.5 to 56.0 gm., with an average of 18.0 gm. (160 cc. molar sodium lactate). Administration of dextrose was usually begun at some time in the second twelve-hour period of treatment, in amounts ranging from 100 to 400 gm. (average, 185 gm.). Three patients received dextrose from the very beginning of treatment, and 3 patients received none at all.

In the past three years two important modifications of the parenteral therapy have been introduced on the advice of Dr. Allan M. Butler. He has pointed out[17-19] the dangers of giving excessive amounts of sodium to patients whose stores of potassium have been depleted and the need for replacing some of the potassium that these patients have lost. In accordance with his views we began to use as the initial parenterally administered solution a saline-and-lactate mixture that had been diluted so that its sodium and chloride content was

TABLE 7. *Diabetic Acidosis, Massachusetts General Hospital, 1942–1944.*

Case No.	Patient	Age	Mental State	Admission Blood Sugar	Admission Blood Carbon-Dioxide Content	Total Insulin Dosage
				mg./100 cc.	*milliequiv./liter*	*units*
1	T. C.	16	Drowsy	193	10.1	92
2	R. B.	33	Drowsy	306	12	296
3	M. H.	35	Drowsy	301	10	335
4	M. M.*	13	Comatose	651		50
5	L. M.	17	Drowsy	524	10.2	174
6	T. C.	16	Drowsy	506	8.2	240
7	J. D.	28	Drowsy	488	7.6	270
8	J. D.	28	Very drowsy	696		674
9	E. M.	18	Conscious	434	7.5	184
10	F. L.*	64	Comatose	1252	9.2	500
11	M. S.	57	Drowsy	542	16.3	516
12	T. G.	17	Drowsy	418	4.7	688
13	J. D.	29	Drowsy	386	8.5	200
14	F. H.	18	Comatose	560	15.7	460
15	L. M.	18	Comatose	360	9.3	728
16	D.G.*	15	Comatose	560	4.6	2400
17	J. R.	16	Drowsy	560	5.6	690
18	J. D.	29	Drowsy	560	10.2	592
19	R. S.	21	Conscious	720	4.4	532
20	E. B.	63	Drowsy	560	7.7	290
21	F. S.	17	Very drowsy	450	4.6	488
22	G. F.*	44	Semicomatose	900	7.3	280
23	M. S.	15	Conscious			320
24	F. S.	17	Drowsy			520
25	T. C.*	18	Very drowsy	400	7.1	660
26	J. O'B.	47	Drowsy			245
27	I. A.	54	Conscious	534		215
28	P. D.*	17	Semicomatose	625	6.0	1120
29	R. J.	16	Drowsy	250		689
30	J. O'B.	47	Conscious			530
31	M. D.	24	Semicomatose	408		850
32	C. M.*	15	Semicomatose	500	5.7	810
33	R. B.	64	Drowsy	156	16.7	446
34	R. V.	44	Conscious	322	11.3	420
Averages		41.8		503	8.9	520

*Died.

isotonic, or even hypotonic, to the sodium and chloride of normal serum, and followed this with a solution containing potassium and phosphate ions.

The "isotonic" solution has the following formula: 0.85 per cent solution of sodium chloride, 1000 cc.; molar sodium lactate, 80 cc.; 5 per cent solution of dextrose in water, 500 cc.; it gives the following approximate concentration in milliequivalents per liter: sodium 150, chloride 100, lactate 50. This solution was used as the initial hydrating fluid in 15 cases. In another 8 cases the initial solution used for parenteral administration was hypotonic to the sodium and the chloride of the serum: sodium, 75 milliequiv. per liter; chloride 50; lactate 25. It is to be emphasized that in these later cases not only was the concentration of sodium and chloride reduced, but the total amount administered was considerably diminished. In terms of normal saline solution, these patients received an average total of 2.0 liters, compared to an average of 4.0 liters given in the earlier cases in this series. It was found that the patients recovered just as satisfactorily on the smaller dose of sodium chloride; indeed, in one respect a definite improvement was noted. Subcutaneous edema, particularly edema of the face, which was commonly noted toward the end of the first twenty-four hours of treatment in those patients receiving 4 or more liters of saline solution, was rarely noted in the patients who received 2 liters or less.

One definite disadvantage in the use of these diluted saline-and-lactate mixtures lies in the fact that we were obliged to use dextrose in water as the diluent because of a hospital rule forbidding flasks of distilled water on the wards. In the case of the "isotonic" solution, the dextrose concentration was 1.5 per cent, and patients received dextrose at the rate of only 10 to 15 gm. per hour. However, in the patients receiving the "hypotonic" solution (which contained twice as much dextrose) it was noted rather frequently that the blood sugar rose during the earlier hours of treatment. The author gained the impression that in general the patients receiving considerable quantities of dextrose early in treatment responded less well than the patients who received little or none. This observation is in agreement with the findings of Franks and others,[4] Root[13] and Lee and his co-workers.[14] For the arguments in favor of the early administration of dextrose the reader is referred to Soskin and Levine,[20] Peters[21] and Mirsky and others.[22] According to Sinden and others[23] a review of the literature indicates that a critical potassium deficiency has developed only in those patients who received considerable amounts of dextrose early in treatment.

At the same time that the "isotonic" solution was introduced (January, 1947), we also began administering solutions containing potassium and phosphorus according to the following formula devised by Butler: sodium lactate, 2.2 gm.; sodium chloride, 0.6 gm.; potassium chloride, 1.0 gm.; potassium dibasic phosphate, 0.5 gm.; 5-10 per cent dextrose solution, 1000 cc. This mixture gives the following approximate concentrations per liter: sodium 30 milliequiv.; potassium 20 milliequiv.; chloride 23 milliequiv.; lactate 20 milliequiv.; and phosphorus

TABLE 8. *Serum Electrolytes.*

	SODIUM (19)*	CHLORIDE (34)	POTASSIUM		PHOSPHORUS
			BEFORE TREATMENT (19)	AFTER TREATMENT (18)†	BEFORE TREATMENT (10)
	milliequiv. /liter	*milliequiv. /liter*	*milliequiv. /liter*	*milliequiv. /liter*	*mg. /100 cc.*
Average	130.7	94.0	5.7	3.4	6.9
Range	111–140	76–108	2.0–8.8	2.2–5.0	2.9–12.5

*Figures in parentheses indicate number of patients on whom determinations were made.
†3 to 24 hours after treatment was started.

90 mg. At the present time it is our policy to use the potassium solution after three to eight hours of treatment with the isotonic saline and lactate solution. As experience with this solution has increased (we have employed it now in 26 cases) we have gained confidence in its use. At first 1 or 2 liters were given, but in the past two years a number of patients have received 4 liters, and 1 patient was given 6 liters of this solution. In several instances we have administered these electrolytes in a concentration exactly doubled, without ill effect.

The possibility of fatal potassium intoxication has been guarded against in several ways. The solution has been withheld at the outset of treatment because of the tendency for serum potassium and inorganic phosphate to be elevated at that time,[11, 12] and it has been withheld in cases of oliguria until the renal function has distinctly improved. In doubtful cases an electrocardiogram has been taken to exclude the presence of a tracing characteristic of a high serum potassium level.[24] The solution has been administered at the slow rate of 3 to 5 cc. per minute.

In such a small series of patients, evaluation of the use of the potassium and phosphate solution is difficult. It may be stated that no harmful reactions were noted, nor was the recovery rate strikingly different from that of the patients treated with saline and lactate solution alone. In no case did the serum potassium rise to levels above normal

during or after the use of this solution. The available metabolic data[12, 17] suggest that the amount of potassium replaced by this therapy represents only a fraction of the quantity lost before treatment. Atchley and others,[12] in their classic balance study of a severe diabetic, withheld insulin for four days and found that the patient lost a total of 385 milliequiv. of potassium during that period.* In the patients in this series, most of whom arrived in the hospital in a much more serious state of acidosis than Atchley's patient was allowed to develop, it is reasonable to suppose that the loss of potassium had been even greater. The discovery[26, 27] that patients recovering from diabetic acidosis can develop a state of acute potassium deficiency that may be fatal adds particular force to the rationale of this therapy.

An account of the intravenous treatment in this series would not be complete without brief mention of two other therapeutic measures. Transfusions of whole blood or plasma in amounts ranging from 500 to 1500 cc. were given to 14 patients whose fall in blood pressure suggested impending shock. It has been our experience in previous years[10] that a fall in blood pressure (particularly the diastolic pressure) during treatment is an ominous prognostic sign, even when the patient otherwise appeared improved. Transfusion in these circumstances appeared to be beneficial.

A solution of buffered phosphate similar to that used by Franks and his co-workers[28] was administered to 1 patient during the first twenty-four hours of treatment and to 2 patients during the second twenty-four-hour period. In each case this was done because of the continued stupor of the patient and because the level of the serum inorganic phosphorus was found to be very low. The marked improvement in the patient's mental status reported by Franks was not observed in these cases.

Orally administered fluids. The importance of early and frequent feeding of patients in diabetic acidosis has often been stressed. In the present series an attempt was made to give each patient nourishment, particularly liquids rich in potassium and phosphorus, as early as possible. Milk, orange juice and beef broth were the fluids generally given.[29] Many of the patients experienced difficulty in swallowing or retaining fluids early in the treatment; most, however, were able to take 100 to 200 cc. hourly in the second twelve-hour period. Six patients were unable to eat anything for the first twenty-four hours or more. One of these patients, whose mental state precluded swallowing, was successfully fed by gastric tube.

Case Reports

Two of the cases in this series, No. 3 and 13, have been reported elsewhere.[19, 30] Both these patients had an initial blood sugar of over 1000 mg., both were anuric and in shock on admission and both had severe cardiac arrhythmias. Both responded slowly only after massive doses of insulin had been given (3600 and 5300 units respectively in the first twenty-four hours). Case 16 was unusual in that the patient was found to have a perforated gastric ulcer. Surgical intervention was successfully undertaken after six hours of intensive treatment of his diabetic acidosis. Case 19 was a case of true insulin resistance.[31] The clinical course is here briefly described:

F. G., a 74-year-old man, was admitted in May, 1949, because of poorly controlled diabetes. While he was in the hospital, the insulin dosage was finally stabilized at 500 units daily. Antibodies for insulin were demonstrated in his serum by Dr. Jacob Lerman. Control of hyperglycemia and ketosis proved to be difficult. On June 27, 1949, he was given only half his usual insulin dose due to an error. This was not discovered for twenty-four hours, when he was found to be in severe acidosis. During the ensuing twenty-two hours he received 17,000 units of insulin in doses of 200 to 500 units every half hour. Although the acidosis was relieved, the blood sugar fell only slightly (460 to 386 mg. per 100 cc.) in this period. He remained in critical condition for another three days.

Second admission. Six months later this patient, who in the interim had been well controlled on 350 units of insulin daily, was again admitted in severe acidosis. On this occasion he was given 10,500 units of insulin in about twelve hours. In the next forty-eight hours he had several mild episodes of hypoglycemia, despite hourly feedings by gastric tube. During this period he remained in critical condition, but gradually rallied and was discharged from the hospital in good condition, taking a daily insulin dose of 650 units.

Case 7 was the single fatality in this series. The history and clinical course were as follows:

K. H., a 75-year-old woman, was admitted on July 17, 1945, with a diagnosis of acute pyelonephritis. Her diabetes had been satisfactorily regulated for several years without insulin. On examination it was found that she was drowsy, restless and disoriented, with marked dehydration and Kussmaul respirations. The blood pressure was 190/80. The urine showed ++ albumin, + sugar, many bacteria and 15 white blood cells per high-power field. There was no acetonuria. The blood sugar was 466 mg. per 100 cc., and the carbon dioxide was 7.0 milliequiv. per liter. The nonprotein nitrogen was 73 mg. per 100 cc.

During the first five hours of treatment she received 530 units of insulin and intravenously administered fluids consisting of 2500 cc. of normal saline solution with 160 cc. molar sodium lactate. Her urine output during this period was 240 cc. and showed only a trace of sugar and no acetone. At the end of five hours the blood sugar was 380 mg. per 100 cc. and the carbon dioxide was 9.2 milliequiv. per liter. She was more lethargic, and soon lapsed into coma. The blood pressure had dropped to 160/50. In the next six hours she received 600 units of insulin, 650 cc. of normal saline and 900 cc. of plasma. The blood sugar fell steadily during this period, and the carbon dioxide rose to 18.2. The urine output improved; 600 cc. was obtained in this period. She developed a moderate generalized edema, and she remained comatose. The blood pressure rose to 280/120.

Through an error in judgment, dextrose was withheld when the blood sugar had fallen to 122 mg. per 100 cc. Thirteen hours after the onset of symptoms she was found to be restless and perspiring profusely. A 25 per cent solution of dextrose was given intravenously, with relief of these symptoms, but it was soon noted that a right hemiplegia had developed. She did not recover consciousness. During the remaining four days of her life, the diabetes was controlled by small doses of insulin given whenever the blood sugar

*Approximately 94 milliequiv. of this total can be accounted for by protein catabolism.[35] The negative nitrogen balance in this experiment was 34.8 gm.

rose above 200 mg. per 100 cc. The carbon dioxide ranged from 14 to 18 milliequiv. per liter and the nonprotein nitrogen remained elevated (57 to 80 mg. per 100 cc.). On the day before death her temperature rose to 105° and she died in peripheral vascular collapse.

A post-mortem examination disclosed a severe grade of acute and chronic pyelonephritis. There was an embolus in the left anterior cerebral artery and infarctions of the left frontal and occipital lobes of the brain.

It is evident, from the persistence of nitrogen retention and of depression of the carbon-dioxide content, that renal failure played an important part in this patient's acidosis. The absence of ketonuria raises some doubt whether diabetes was at all responsible for her condition. A blood ketone determination would have helped to settle this point. Because she was treated for diabetic acidosis, it was decided to include her case in this report, even though the acidosis had been relieved some time before her death.

Clinical Course

In 66 of the 67 cases, the blood sugar had dropped to 250 mg. per 100 cc. or lower in the first twenty-four hours. In all cases, significant ketosis had been relieved within twenty-four hours. For the most part the patients were very much improved in all respects at the end of this time; however, there were at least 10 patients whose condition remained poor for another one to three days, despite normal blood-sugar and carbon-dioxide levels.

A number of complications occurring within the first twenty-four-hour period are worthy of note. Anuria was present in Cases 3 and 13, lasting six and four hours respectively. Oliguria, with an output of 10 to 30 cc. per hour, was noted for varying periods in 6 other cases. Various disturbances of cardiac rhythm were observed. Simple tachycardia was seen frequently; auricular fibrillation was noted in 3 cases and auricular flutter in 1 case. The blood pressure frequently began to fall after several hours of treatment and was often accompanied by a temporary worsening of the patient's appearance and mental status. After the publication in 1946 of Holler's[26] article on the syndrome of potassium deficiency in diabetic acidosis, all patients were carefully watched for signs of muscular weakness and respiratory embarrassment, but a definite diagnosis of this condition was not made in any case. In a number of cases electrocardiograms showed the low T waves and depressed ST segments that are characteristically found in patients with potassium depletion.[22] It is possible that this finding and the fall in blood pressure occasionally seen represent early manifestations of potassium deficiency, an impression that is confirmed by Frenkel's[27] description of the cardiovascular manifestations in this syndrome.

Comment

It is not possible accurately to evaluate the various factors that led to the improvement in our mortality rate after 1944. The author wishes, however, to emphasize the aspects of treatment that he believes were chiefly responsible. Most important were the teamwork of the hospital staff, the overall medical care, which included prompt initiation of treatment, constant vigilance for and treatment of complications, frequent consultation and a policy of never leaving the patient unattended by a doctor until all possible danger was passed. Next in importance was the administration of large doses of insulin, made possible by having twenty-four-hour laboratory service for blood-sugar determinations. The institution of oral feeding at the earliest possible moment and care in the selection and administration of parenterally given fluids also contributed to the favorable results.

Summary

The clinical data and the treatment of 67 cases of diabetic acidosis are presented. In this series there was one death.

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References

1. Baker, T. W. Clinical survey of 103 consecutive cases of diabetic coma. *Arch. Int. Med.* **58**:373-405, 1936.
2. Collen, M. F. Mortality in diabetic coma. *Arch. Int. Med.* **70**:347-368, 1942.
3. Dillon, E. S., and Dyer, W. W. Factors influencing prognosis in diabetic coma. *Ann. Int. Med.* **11**:602-617, 1937.
4. Franks, M., Berris, R. F., Kaplan, N. O., and Myers, G. B. Metabolic studies in diabetic acidosis. I. Effect of early administration of dextrose. *Arch. Int. Med.* **80**:739-762, 1947.
5. Joslin, E. P., et al. *The Treatment of Diabetes Mellitus.* 861 pp. Philadelphia: Lea & Febiger, 1946.
6. Rabinowitch, I. M., Fowler, A. F., and Bensley, E. H. Diabetic coma (investigation of mortalities and report of severity index for comparative studies). *Ann. Int. Med.* **12**:1403-1428, 1939.
7. Almy, T. P., Swift, K., and Tolstoi, E. Treatment of diabetic acidosis and diabetic coma. *J. A. M. A.* **129**:863-868, 1945.
8. Marble, A. Personal communication.
9. Case Records of the Massachusetts General Hospital (Case 37031). *New Eng. J. Med.* **244**:101-105, 1951.
10. Harwood, R. Unpublished data.
11. Guest, G. M., and Rapoport, S. Electrolytes of blood plasma and cells in diabetic acidosis and during recovery. *Proc. Am. Diabetes A.* **7**:97-115, 1947.
12. Atchley, D. W., et al. On diabetic acidosis: detailed study of electrolyte balances following withdrawal and reestablishment of insulin therapy. *J. Clin. Investigation* **12**:297-326, 1933.
13. Root, H. F. Use of insulin and abuse of glucose in treatment of diabetic coma. *J. A. M. A.* **127**:557-564, 1945.
14. Lee, J., Naidoo, D., and Torrens, J. A. Diabetic coma: treatment with and without early administration of glucose. *Brit. M. J.* **1**: 565-568, 1949.
15. Sheppard, J. G. H. Case of diabetic coma treated with 56,000 units of insulin. *Brit. M. J.* **1**:576, 1949.
16. Yannet, H. Experimental study of pathogenesis of cerebral changes following prolonged insulin hypoglycemia. *Arch. Neurol. & Psychiat.* **42**:395-402, 1939.
17. Butler, A. M., et al. Metabolic studies in diabetic coma. *Tr. A. Am. Physicians* **60**:102-109, 1947.
18. Butler, A. M. Parenteral fluid in diabetic coma. *Acta pediat. Scandinav.* **38**:59-69, 1949.
19. *Idem.* Discussion in "Medical Grand Rounds." *Am. Pract.* **2**:606, 1948.
20. Soskin, S., and Levine, R. Relationship between blood sugar level and rate of sugar utilization, affecting theories of diabetes. *Am. J. Physiol.* **120**:761-770, 1937.
21. Peters, J. P. Use of carbohydrate in diabetic acidosis. *Am. J. Digest. Dis.* **13**:127-130, 1946.
22. Miraky, I. A., Heiman, J. D., and Broh-Kahn, R. H. Antiketogenic action of glucose in absence of insulin. *Am. J. Physiol.* **118**:290-296, 1937.
23. Sinden, R. H., Tullis, J. L., and Root, H. F. Serum potassium levels in diabetic coma. *New Eng. J. Med.* **240**:502-505, 1949.

24. Tarail, R. Relation of abnormalities in concentration of serum potassium to electrocardiographic disturbances. *Am. J. Med.* **5**:828-837, 1948.

25. Reifenstein, E. C., Jr., Albright, F., and Wells, S. L. Accumulation, interpretation, and presentation of data pertaining to metabolic balances, notably those of calcium, phosphorus, and nitrogen. *J. Clin. Endocrinol.* **5**:367-395, 1945.

26. Holler, J. W. Potassium deficiency occurring during treatment of diabetic acidosis. *J. A. M. A.* **131**:1186-1189, 1946.

27. Frenkel, M., Groen, J., and Willebrands, A. F. Low serum potassium level during recovery from diabetic coma, with special reference to its cardiovascular manifestations. *Arch. Int. Med.* **80**:728-738, 1947.

28. Franks, M., Berris, R. F., Kaplan, N. O., and Myers, G. B. Metabolic studies in diabetic acidosis: effect of administration of sodium phosphate. *Arch. Int. Med.* **81**:42-55, 1948.

29. McCance, R. A., and Widdowson, E. M. *The Chemical Composition of Foods.* 156 pp. Brooklyn, New York: Chemical Publishing Company, 1947.

30. Gorman, R. V., Harwood, R., and White, P. D. Successful treatment of severe diabetic coma complicated by chronic laryngeal obstruction: report of case. *New Eng. J. Med.* **234**:500-503, 1946.

31. Smelo, L. S. Insulin resistance. *Proc. Am. Diabetes A.* **8**:77-111, 1948.

32. Martin, H. E., and Wertman, M. Electrolyte changes and electrocardiogram in diabetic acidosis. *Am. Heart J.* **34**:646-662, 1947.

CARBON-DIOXIDE INTOXICATION IN EMPHYSEMA: EMERGENCY TREATMENT BY ARTIFICIAL PNEUMOPERITONEUM*

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WHEN oxygen is administered to a patient with chronic anoxemia, an elevation of the carbon-dioxide content and combining power of the blood usually occurs. In patients with marked pulmonary emphysema and fibrosis, this elevation is occasionally of profound degree, and a characteristic sequence of events ensues. The features of the clinical syndrome are headache, cutaneous vasodilatation, irrationality, stupor and coma. It is thought that these manifestations are due to carbon-dioxide intoxication. The chain of events leading to carbon-dioxide retention is believed to be as follows: removal of the anoxemic stimulus to respiration by the administered oxygen, reduced pulmonary ventilation, increase in the partial pressure of carbon dioxide in the pulmonary alveoli and increase in the carbon-dioxide content of the blood. A vicious circle results from further depression of respiration due to high partial pressure of carbon dioxide in the blood.

It is the purpose of this report to describe the syndrome in detail on the basis of two severe cases and to present a form of therapy that may occasionally prove life-saving.

CASE REPORTS

CASE 1. B. T., a 40-year-old man, was admitted to the Johns Hopkins Hospital on December 21, 1947, because of shortness of breath. For five years the patient had had an unproductive cough, as well as moderate exertional dyspnea. For one year he had suffered from frequent frontal headaches. In May, 1947, swelling of the ankles developed for the first time and dyspnea increased. In September cyanosis appeared and dyspnea became totally incapacitating.

On admission the patient was plethoric, cyanotic and moderately dyspneic at rest but could lie flat with reasonable comfort. The chest was markedly emphysematous. Breath sounds were distant, with occasional asthmatic wheezes. Percussion of the heart was unsatisfactory. There was no cardiac impulse. Heart sounds were faint at the base. At the apex the first sound was strikingly split. The blood pressure was 150/100. The liver was 4 cm. below the right costal margin. There was no peripheral edema at the time of admission.

Laboratory examination on admission revealed a hemoglobin of 17.5 and a red-cell count of 7,380,000, with a hematocrit of 65, normal cell indices and 10 per cent reticulocytes. The white-cell count was 5500, with a normal differential count, the venous pressure 68 mm. of saline solution, the circulation time (Decholin) 15 seconds and the vital capacity 1.9 liters and the blood nonprotein nitrogen 44 mg. per 100 cc. X-ray films of the chest revealed slight generalized cardiac enlargement with prominence of vessels at lung hili; electrocardiograms showed marked right-axis deviation, right heart strain and the cor-pulmonale type of P waves.

One week after admission the patient was digitalized. During the five days after digitalization, rather severe right heart failure developed. Digitalis was discontinued and oxygen by mask instituted.

Forty-eight hours before death the patient was confused and complained of a severe generalized headache. During the course of the afternoon he gradually became less responsive. By early evening he was unconscious. Pulmonary edema cleared dramatically after venesection of 250 cc. of blood. During the night respirations dropped to 4 per minute for a brief period. On the following day the serum carbon-dioxide combining power was more than 40 milliequiv. (90 vol. per cent).§ Serum chlorides measured 91.8 milliequiv. Aminophylline was administered intramuscularly at regular intervals and mercupurin, 2.2 cc., was given. The blood pressure, which was 180/110 in the early stages of failure, fell to 80/60. That evening dullness at the left base with tubular breathing was discerned. Penicillin, previously given prophylactically, was increased to 100,000 units given intramuscularly every two hours. A bedside radiograph showed clouding of the left lower lung field. At 1:00 p.m. on the following day the blood pressure was 60/20. The patient died at 2:50 p.m., twelve days after digitalization and five days after oxygen therapy was instituted.

The terminal unconsciousness was interpreted as carbon-dioxide narcosis. It began with headache and confusion when oxygen was administered and progressed into coma. A reduced rate of respiration while receiving oxygen was observed.

Significant autopsy findings were limited to the heart and lungs. Both lungs were soggy and heavy but nevertheless floated in water. Together they weighed 2300 gm. There were several small emphysematous blebs (the largest 10 mm. in diameter) on the surface of the lungs. Grossly the alveoli appeared widely dilated. There were firm areas of consolidation in the left lower lobe.

The heart was enlarged, weighing 560 gm. The tricuspid and pulmonic valves were slightly dilated, measuring 130 and 80 mm. respectively. Both the right and left ventricles were moderately dilated and hypertrophied. The liver weighed 1830 gm.

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§All carbon-dioxide combining-power determinations were made on venous blood.

Pulmonary emphysema was confirmed histologically. The pulmonary consolidation had the characteristic appearance of aspiration pneumonia.

CASE 2. *First admission.* F. S., a 56-year-old man, was admitted to the Baltimore Marine Hospital in December, 1949, because of marked dyspnea and cyanosis. His only significant past illness was thirty years previously, when he had "influenza." Moderate exertional dyspnea and cough productive of mucopurulent sputum began ten years before admission. He was able to work until four years prior to admission, when his dyspnea became incapacitating.

In December, 1949, he was admitted to the Baltimore Marine Hospital, complaining of edema of one week's duration. He had severe attacks of cyanosis during paroxysms of coughing. On admission he was markedly dyspneic at rest. The blood pressure was 155/105, the pulse rate was 110 per minute and the respiratory rate was 30 per minute. The skin showed a dusky, cyanotic color, with dilatation of the superficial vessels of the face. The chest was markedly emphysematous. Breath sounds were diminished over both lung fields, with sibilant rales during the prolonged expiratory phase and medium moist rales at both lung bases posteriorly. The heart was slightly enlarged to percussion. The liver was palpable 5 cm. below the right costal margin. There was marked dependent edema extending posteriorly to the level of the costovertebral angles.

Routine blood chemical determinations and hemogram were within normal limits. On admission the venous pressure was equal to 250 mm. of saline solution, and the circulation time was 32 seconds (Decholin). Chest x-ray examination showed prominent hilar vascular markings and pleural thickening at the costophrenic angles. The cardiac silhouette was at the upper limit of normal in size. The electrocardiogram showed right-axis deviation and tall P waves compatible with cor pulmonale and right heart strain. Treatment with a low-salt diet and mercurial diuretics was accompanied by a 55-pound weight loss in twenty-one days. Cardiac catheterization, performed after the loss of edema, showed a pulmonary-artery pressure of 65/40, a mean pulmonary-artery pressure of 50, and a right-ventricular pressure of 70/8. Arterial oxygen saturation was 89 per cent. Venous pressure at the time of discharge was equal to 120 mm. of saline solution and the circulation time was 19 seconds (Decholin).

Second admission. During the five-week interval the patient ate salt freely and took no medication. Four days before admission there was an exacerbation of dyspnea at rest, with marked cyanosis, weakness, lassitude and anorexia. When seen on March 4, 1950, he was very weak and lethargic, speaking with great difficulty. There were sibilant rales over both lung fields, with coarse moist rales at the bases posteriorly. The liver edge was palpable 3 cm. below the right costal margin. There was slight pedal edema bilaterally. The administration of aminophylline intravenously, of adrenalin subcutaneously and of oxygen by mask was followed by lessening of the cyanosis. However, the patient gradually became more lethargic and finally was unresponsive.

He was treated with aminophylline intravenously at six- to eight-hour intervals and was placed in an oxygen tent with 50 per cent concentration of oxygen. During the ensuing four days his color was good, but he remained in a semicomatose state. When taken from the oxygen tent for short periods he became cyanotic, struggled aimlessly and developed a tachycardia. On the fourth hospital day the carbon-dioxide combining power was 36.9 milliequiv.

In an attempt to produce more adequate ventilation, the patient was placed in a Drinker–Emerson respirator and given nasal oxygen. With the aid of the respirator, operating at pressures alternating between +8 and −15 cm. of water, ventilation was improved, with some clearing of the sensorium. Twelve hours after he was placed in the respirator the carbon-dioxide combining power was 33.3 milliequiv. and the serum chloride was 82 milliequiv. Fluids containing a total of 27 grams of sodium chloride were given parenterally during the ensuing seventy-two hours. The patient received 0.5 gm. of aminophylline in a retention enema every six hours and intermittent intravenous aminophylline with the parenterally administered fluid. However, his clinical course was one of progressive deterioration. Cyanosis returned, and he was completely comatose for about forty-eight hours.

On March 11 the patient was *in extremis* with marked cyanosis and deep coma and with the blood pressure ranging around 120/100. The carbon-dioxide combining power was 44.5 milliequiv. and serum chloride was 85.6 milliequiv. Throughout the period in the respirator it was noted that the thoracic cage barely moved with respiration. Furthermore, the abdomen was lax and scaphoid, and the respirator appeared to be ineffective in producing respiratory excursion of the diaphragm.

Artificial pneumoperitoneum was instituted at 5:00 p.m. on March 11, 2250 cc. of air being given with a closing pressure of +5 cm. of water. During institution of the initial pneumoperitoneum, respirations increased in depth and the respiratory rate decreased from 40 to 28, there was improvement in color and the patient was now attempting to cough, resisting aspiration vigorously. Four hours after the institution of artificial pneumoperitoneum the carbon-dioxide combining power was 35.6 milliequiv. Six hours after the initial pneumoperitoneum he was given an additional 1750 cc. of air with a closing pressure of +7 cm. of water. His color had shown further improvement and the sensorium was markedly cleared; he was able to cough and was attempting to talk. Oxygen therapy and artificial respiration were discontinued at this time.

Thirty hours later the carbon-dioxide combining power was 28.4 milliequiv. He was able to sit on the side of the bed, and he stated that he was hungry and was able to eat. During the two weeks following institution of artificial pneumoperitoneum he showed progressive improvement, having no dyspnea at rest and moderate improvement in exertional dyspnea. Venous pressure was 120 mm. of saline solution, circulation time 17 seconds (Decholin) and three-second vital capacity 1300 cc. There was very little discomfort from the pneumoperitoneum. The diaphragm, which had no detectable motion prior to pneumoperitoneum, was elevated one and a half intercostal spaces posteriorly and moved through a 3-cm. range during forced breathing (Fig. 1).

Review of the Literature

Narcosis caused by carbon dioxide has been known since the 1820's, when Henry Hill Hickman, a pioneer anesthesiologist, performed operations on animals rendered insensible by the gas.[1]

In the past it was doubted that carbon-dioxide retention in human beings could reach proportions to cause death. Writing in 1926, D. D. Van Slyke[2] stated: "Medical and lay literature contains numerous cases of death from oxygen lack, in respiratory disease, in high altitudes, in carbon-monoxide poisoning, but it is doubtful that it contains any case of death due primarily to impaired respiratory ability to excrete carbonic acid."

Gradually, however, evidence accumulated to indicate that retention of carbon dioxide in toxic amounts may occur in patients with profound impairment of pulmonary ventilation, and simultaneously the mechanism of this retention was elucidated.

In 1921 Scott[3] demonstrated that persons with far-advanced pulmonary emphysema present a unique situation in which the regulatory mechanism for respiration is quite insensitive to carbon-dioxide excess and the primary stimulus to respiration is oxygen deficit. Comroe and Schmidt[4] state that the carotid body "is only stimulated by anoxia of all degrees and even enormous increases in CO_2 tension do not appreciably depress it, whereas the cells of the center are depressed both by severe anoxia and by excessive hypercapnia."

Marshall and Rosenfeld[5] also demonstrated that administration of oxygen under certain conditions of depression of the respiratory center may further depress respirations. In 1921 Barach and Woodwell[6] observed increases in the blood carbon-dioxide content of cardiac patients receiving oxygen, and Barach and Richards[7] confirmed this observation in 1931. Berconsky[8] and Knipping[9, 10] described the rise in blood and alveolar carbon-dioxide tension with oxygen administration to patients with chronic pulmonary and cardiac disease and attributed it to reduced pulmonary ventilation secondary to removal of the anoxic stimulus to respiration. tion of 50 per cent oxygen in patients with a previously existing chronic anoxia may temporarily produce a profound disturbance in mental functioning." Barach believes that most of these patients will become acclimatized to the increased oxygen tension in two to four days, with disappearance of the mental disturbance.

There are several recent references[14-20] to the syndrome under discussion, all but one having been published from the laboratories of Richards and Barach.

Davies and Mackinnon[21] have recently described two patients with cor pulmonale who developed

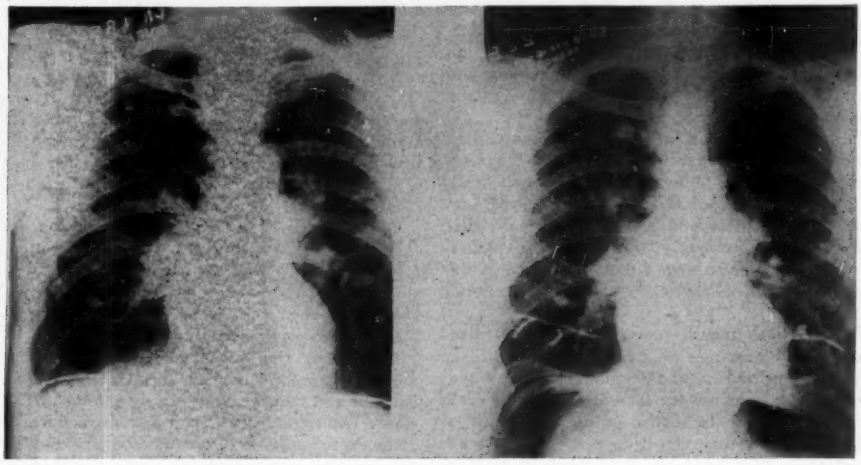

FIGURE 1. *X-ray Films of Chest in Case 2.*

On left: chest in maximum inspiratory position before pneumoperitoneum; position of diaphragm in maximum expiration indicated by white lines. On right: same after pneumoperitoneum, in maximum inspiration with position of diaphragm in maximum expiration indicated by white lines.

The full clinical picture and its pathologic physiology were delineated by Richards and Barach in 1932.[11] These authors attributed the coma seen in carbon-dioxide intoxication to the high carbon-dioxide content of the blood and believed the mechanism of the carbon-dioxide retention to be that discussed in detail in this report.

Brown,[12] studying the possible effects of high concentrations of carbon dioxide in submarine personnel, subjected normal persons to carbon-dioxide concentrations of 5.5 to 12.4 vol. per cent. Marked dyspnea, dizziness, flushing and sweating of the face and a feeling of stupefaction and apprehension over impending collapse ensued. The author concluded that no subject could tolerate 10 per cent carbon dioxide for periods greater than ten minutes without losing consciousness.

In 1941 Barach[13] amplified the description of this syndrome. "A report is made of a phenomenon not generally recognized, namely, that the inhala- neurologic manifestations when oxygen was administered by B.L.B. mask. One patient developed "uncontrollable myoclonic movements," profuse sweating of the head and neck and a sensation of fullness in the head. The symptoms disappeared when oxygen was discontinued. With oxygen administration the second patient passed into coma and died four hours after oxygen was given.

Although they suspected that oxygen administration had some effect on the reaction to carbon dioxide, Davies and Mackinnon[21] believed that the neurologic manifestations were due to increased intracranial pressure, as evidenced by elevation of cerebrospinal-fluid pressure.

The subject of oxygen poisoning and its possible relation to the syndrome under discussion is an important one. There is much evidence[22-26] attesting the harmfulness to animals of high concentrations of oxygen. With high concentration of oxygen at atmospheric pressure, the primary pathologic

changes are confined to the lungs and are essentially pulmonary edema followed by consolidation and later pneumonitis. Only when animals are subjected to higher tensions of oxygen (3 to 4 atmospheres) do convulsions occur.

In human beings the effects of breathing 100 per cent oxygen over prolonged periods of time are equivocal. The investigations of Behnke and his co-workers[27] and of Comroe and others[28] suggest that respiratory-tract irritation may occur. With the concentrations of oxygen attainable by either tent or mask there are apparently no deleterious effects except indirectly, as in the syndrome under discussion.

Clinical Manifestations

The clinical manifestations are: headache, cutaneous vasodilatation, respiratory depression and mental dysfunction, the most striking form of the last being coma.

The cerebral vasculature is dilated by carbon dioxide,[29] and presumably this is the mechanism of the cephalalgia. Others[12] have described headaches caused by carbon dioxide. Elevation of cerebrospinal-fluid pressure[22] and papilledema[30] that may occur are probably the result of cerebral vasodilatation. Flushing from cutaneous vasodilatation produced by carbon dioxide has been described.[12, 21]

The cerebral manifestations — confusion, irrationality and coma, — are most probably a direct result of increased carbon-dioxide tension. Whenever measured, the oxygen saturation in these cases has been found to be higher during the period of carbon-dioxide intoxication, since it is oxygen administration that produces the carbon-dioxide retention.

Barach[13, 14] states that the mental dysfunction and other manifestations disappear as the patients "become acclimatized to the increased oxygen tension." In the cases reported here there was no evidence of acclimatization.

Hypertension from carbon dioxide is familiar to the anesthesiologist[32] and to the physiologist.[12] The hypertension in Case 1 may, however, have been due to heart failure.

In the late stages of the syndrome there may be further depression of respiration, with a progressive fall in arterial oxygen saturation. Depression of respiration at this time is probably due to the direct effect of the high partial pressure of carbon dioxide[4, 33, 34] on the respiratory center.

Patients with carbon-dioxide intoxication in coma commonly die from pulmonary and other complications and not from the primary poison. This was well demonstrated by the autopsy findings in Case 1, in which aspiration pneumonitis was a striking feature. Therefore the therapeutic problem resolves itself into the prevention of these pulmonary complications until a more direct therapeutic approach, as discussed below, can be taken.

Chemical Alterations

The chemical changes that occur with carbon-dioxide intoxication are a rise in the serum bicarbonate (that is, carbon-dioxide combining power) and a fall in serum chlorides. Maintenance of the blood pH in a normal range depends on a proper ratio of bicarbonate to carbonic acid, as described by the Henderson–Hasselbalch equation. With carbon-dioxide retention the carbonic acid of the blood rises. As a compensatory mechanism, chloride is excreted by the kidney, thereby providing more base for combination with bicarbonate ion. Since the ratio of bicarbonate to carbonic acid approaches the normal, only mild acidosis is to be expected with carbon-dioxide intoxication. This lack of consistent depression of arterial blood pH was recently reported by Comroe and associates.[20] Barach,[18] however, has apparently been more impressed with the depression of blood pH in this syndrome and believes this to be the cause of the mental changes.

On the basis of present information concerning this syndrome, it appears that the clinical manifestations result from the high carbon-dioxide tension per se. It must be concluded, however, that the precise chemical pathogenesis of this syndrome has not been established.

Concerning therapy, there is no evidence that ammonium chloride will significantly increase serum chloride and reduce serum bicarbonate in this situation. The administration of sodium lactate in an attempt to increase serum bicarbonate and serum pH has been reported to produce improvement in mental symptoms.[18] If there is no improvement in pulmonary ventilation, the electrolyte disturbance will probably recur. Furthermore, there will have been an increase in the total serum electrolytes. The consequent aggravation of the tendency toward edema may further complicate therapy. It is not implied, however, that maintenance of proper fluid balance is not important. Sodium chloride is necessary for the re-establishment of acid-base balance that accompanies more adequate pulmonary ventilation.

Emergency Treatment by Artificial Pneumoperitoneum

It has been emphasized by Barach[13, 14] that the syndrome of carbon-dioxide intoxication is usually temporary and reversible. This is the usual outcome when the process underlying the development of the syndrome is correctible, as is the case with congestive heart failure and bronchospasm. Patients with far-advanced pulmonary emphysema and fibrosis present a different problem. Generally it is not possible to correct their ventilatory insufficiency by the usual therapeutic measures, and once the syndrome has advanced to the stage of coma the

outcome is usually fatal. It hardly seems possible that acclimatization to the excessively high carbon-dioxide content of the arterial blood that is seen in the terminal stages of the syndrome could occur. Therefore the only means of correcting the comatose state is through the establishment of more adequate pulmonary ventilation.

One means of improving pulmonary ventilation is by means of artificial respiration, using the Drinker respirator. However, the benefit that can be attained is definitely limited, because of the difficulty in synchronizing the patient's attempts at respiration with the cycle of the respirator. Secondly, the primary distention of the lungs, fixation of the bony thorax and loss of elastic recoil of the lung severely limit the expiratory function of the respirator, even when it is operated at a relatively high positive pressure during the expiratory phase.

The treatment of pulmonary emphysema with artificial pneumoperitoneum was first introduced by Reich[35] in 1924, and the subsequent reports of Piaggio–Blanco[36] and Monaldi[37] and the findings of Furman and Callaway[38] indicate that this form of therapy provides definite benefit in a significant number of cases.

The beneficial effects of artificial pneumoperitoneum are attributed to its effectiveness in restoring toward normal the ratio of residual air to total lung volume and in elevating the diaphragm to a more normal expiratory position. This elevation of the diaphragm allows it to participate more effectively in the respiratory cycle (Fig. 1).

In carbon-dioxide intoxication the consequences of these alterations in respiratory function are: reduction in size of the inadequately ventilated portion of the lung, in which there is stagnation of large amounts of carbon dioxide and increase in the effective volume of tidal air, with the result that larger amounts of carbon dioxide are eliminated.

The symptoms of carbon-dioxide intoxication are profound manifestations of pulmonary emphysema. In Case 2, the prompt clinical improvement and concomitant lowering of the carbon-dioxide combining power of the plasma were most striking.

Summary

Two cases of a syndrome of carbon-dioxide intoxication in patients with emphysema are reported. The manifestations were headache, cutaneous vasodilatation, irrationality, stupefaction and coma. Elevation of serum carbon-dioxide combining power, together with depression of serum chloride, was observed. In one case, after seventy-two hours of profound coma, artificial pneumoperitoneum was immediately effective in restoring normal mental function and correcting the chemical abnormality.

References

1. Thompson, C. J. S. Henry Hill Hickman: forgotten pioneer of anesthesia. *Brit. M. J.* **1**:843-845, 1912.
2. Van Slyke, D. D. *Factors Affecting the Distribution of Electrolytes, Water and Gases in the Animal Body.* 62 pp. Philadelphia: J. B. Lippincott Company, 1926. P. 60.
3. Scott, R. W. Observations on pathologic physiology of chronic pulmonary emphysema. *Arch. Int. Med.* **26**:544-560, 1920.
4. Comroe, J. H., Jr., and Schmidt, C. F. Part played by reflexes from carotid body in chemical regulation of respiration in dog. *Am. J. Physiol.* **121**:75-97, 1938.
5. Marshall, E. K., Jr., and Rosenfeld, M. Depression of respiration by oxygen. *J. Pharmacol. & Exper. Therap.* **57**:437-457, 1936.
6. Barach, A. L., and Woodwell, M. N. Studies in oxygen therapy with determinations of blood gases. I. In cardiac insufficiency and related conditions. *Arch. Int. Med.* **28**:367-393, 1921.
7. Barach, A. L., and Richards, D. W., Jr. Effects of treatment with oxygen in cardiac failure. *Arch. Int. Med.* **48**:325-347, 1931.
8. Berconsky, I. La función hemo-respiratoria en los "cardiacos negros de Ayerza." *Semana méd.* **1**:1569-1593, 1933.
9. Knipping, H. W., Lewis, W., and Moncrieff, A. Über die Dyspnoe. *Beitr. z. Klin. d. Tuberk.* **79**:1-57, 1931.
10. Knipping, H. W. Dyspnoe. *Beitr. z. Klin. d. Tuberk.* **82**:133-152, 1933.
11. Richards, D. W., Jr., and Barach, A. L. Effects of oxygen treatment over long periods of time in patients with pulmonary fibrosis. *Am. Rev. Tuberc.* **26**:253-260, 1932.
12. Brown, E. W. Physiological effects of high concentrations of carbon dioxide. *U. S. Nav. M. Bull.* **28**:721-734, 1930.
13. Barach, A. L. Effect of low and high oxygen tensions on mental functioning. *J. Aviation Med.* **12**:30-38, 1941.
14. *Idem.* Physiological treatment of pulmonary emphysema. *Am. Pract.* **2**:771-778, 1948.
15. *Idem. Physiologic Therapy in Respiratory Diseases.* Second edition. 408 pp. Philadelphia: J. B. Lippincott Company, 1948.
16. Ferrer, M. I., Harvey, R. M., Cathcart, R. T., Webster, C. A., Richards, D. W., Jr., and Cournand, A. Some effects of digoxin upon heart and circulation in man. *Circulation* **1**:161-186, 1950.
17. Baldwin, E. DeF., Cournand, A., and Richards, D. W., Jr. Pulmonary insufficiency. III. Study of 122 cases of chronic pulmonary emphysema. *Medicine* **28**:201-237, 1949.
18. Barach, A. L. Treatment of anoxia in clinical medicine. *Bull. N. Y. Acad. Med.* **26**:370-383, 1950.
19. Richards, D. W., Jr. Inhalational therapy in cardiac diseases: cardiac failure. *Bull. New York Acad. Med.* **26**:384-394, 1950.
20. Comroe, J. H., Jr., Bahnson, E. R., and Coates, E. O., Jr. Mental changes occurring in chronically anoxemic patients during oxygen therapy. *J. A. M. A.* **143**:1044-1048, 1950.
21. Davies, C. E., and Mackinnon, J. Neurological effects of oxygen in chronic cor pulmonale. *Lancet* **2**:883-885, 1949.
22. Barach, A. L., Eckman, M., Tribe, E., Oppenheimer, C. R., Jr., and Soroka, M. Observations on methods of increasing resistance to oxygen poisoning and studies of accompanying physiological effects. *Am. J. Physiol.* **142**:462-475, 1944.
23. Smith, J. L. Pathological effects due to increase of oxygen tension in air breathed. *J. Physiol.* **24**:19-35, 1899.
24. Karsner, H. T. Pathological effects of atmospheres rich in oxygen. *J. Exper. Med.* **23**:149-170, 1916.
25. Binger, C. A. L., Faulkner, J. M., and Moore, R. L. Oxygen poisoning in mammals. *J. Exper. Med.* **45**:849-864, 1927.
26. Barach, A. L. Effects of atmospheres rich in oxygen on normal rabbits and on rabbits with pulmonary tuberculosis. *Am. Rev. Tuberc.* **13**: 293-316, 1926.
27. Behnke, A. R., Shaw, L. A., Shilling, C. W., Thomson, R. M., and Messer, A. C. Studies on effects of high oxygen pressure; effect of high oxygen pressure upon carbon-dioxide and oxygen content, acidity, and carbon-dioxide combining power of blood. *Am. J. Physiol.* **107**:13-28, 1934.
28. Comroe, J. H., Jr., Dripps, R. D., Dumke, P. R., and Deming, M. Oxygen toxicity: effect of inhalation of high concentrations of oxygen for twenty-four hours on normal men at sea level and at simulated altitude of 18,000 feet. *J. A. M. A.* **128**:710-717, 1945.
29. Brazier, M. A. B. Physiological effects of carbon dioxide on activity of central nervous system in man with special reference to problem of high altitude flying: review. *Medicine* **22**:205-221, 1943.
30. Simpson, T. Papilloedema in emphysema. *Brit. M. J.* **2**:639-641, 1948.
31. Prausnitz, C. Untersuchungen über die Einwirkung höherer Kohlensäurekonzentrationen der Atemluft. *Med. Klin.* **24**:282-285, 1928.
32. Leake, C. D., and Waters, R. M. Anesthetic properties of carbon dioxide. *Anesth. & Analg.* **8**:17-19, 1929.
33. Sollman, T. *A Manual of Pharmacology.* Fifth edition. 1190 pp. Philadelphia: W. B. Saunders Company, 1936.
34. Miller, F. A., Brown, E. B., and Varco, R. L. Certain effects in dogs of inspiring 15-30 per cent carbon dioxide. *Federation Proc.* **9**:89, 1950.
35. Reich, L. Der Einfluss des Pneumoperitoneums auf das Lungenemphysem. *Wien. Arch. f. inn. Med.* **8**:245-260, 1924.
36. Piaggio-Blanco, R. A., Piaggio-Blanco, R. O., and Caimi, R. A. Mejorías sintomáticas del enfisema por el neumoperitoneo. *Arch. urug. de med., cir. y especialid.* **10**:273-283, 1937.
37. Monaldi, E. Il diaframma nella regolazione dei rapporti tra torace e addome; studio fisio-clinico e impostazione del pneumoperitoneo in terapia. *Rev. argent. de tuberc.* **3**:161-174, 1937.
38. Furman, R. H., and Callaway, J. J. Artificial pneumoperitoneum in treatment of pulmonary emphysema: preliminary report. *Dis. of Chest* **18**:232-243, 1950.

BACITRACIN IN DERMATOLOGY: ITS EFFECTIVENESS IN TOPICAL THERAPY

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THIS REPORT, covering a period of eight successive months, presents significant clinical data obtained after the application of bacitracin topical therapy in 83 cases, 75 of which represent a wide variety of the accessible pyodermas.

A large percentage of these cases had been unresponsive to numerous other therapeutic routines and agents previously administered. Response, however, to either an ointment consisting of 500 units of bacitracin per gm. of petrolatum or to compresses with an optional concentration of 500 units of bacitracin per cc. was rapid and effective and led to no recurrence in an astonishing number of cases. Cures were effected in 61.5 per cent and there was marked improvement in 30.1 per cent and moderate improvement in 6 per cent. Bacitracin was ineffective in one case of folliculitis and one of pyoderma, although similar cases responded adequately.

There is ample evidence in the literature that a high allergenic index (disproportionate to both their systemic and parenteral values) accompanies the topical administration of several otherwise highly effective bactericidal agents. Results obtained in this present survey emphasized the observations of previous investigators concerning the low allergenic index of bacitracin in topical use. Sensitization appeared in 1 out of the 83 cases. This case, in a man of sixty-three years, was manifested by a localized dermatitis on the lower legs, and occurred during treatment of a secondary infection involving an old ulcer of traumatic origin on the right leg. Four days after bacitracin treatment was instituted a dermatitis appeared over most of the involved lower right leg and also over the left middle tibia. After the rash appeared treatment was discontinued; two days later the rash disappeared. A second case of sensitization was noted in a twenty-seven-year-old woman during the treatment of an extensive infectious eczematoid dermatitis of six weeks' duration, involving the fingers of both hands. On the second day of treatment with bacitracin ointment the patient developed a blotchy facial dermatitis that was interpreted as probably a form of autosensitization not due to bacitracin. The facial dermatitis slowly faded out; bacitracin therapy was resumed and the hand dermatitis cleared in six days without recurrence of the facial rash.

Bacitracin, an antibiotic reported by Johnson, Anker and Meleney,[1] in 1945, is produced by a specific strain of the *B. subtilis* group of organisms; it was originally obtained from tissue debrided from a compound fracture of the tibia. It is active in vitro chiefly against gram-positive streptococci and staphylococci. The gonococcus, pneumococcus, spirochete of syphilis, diphtheria bacillus and diphtheroids are also susceptible to its action. Studies in vivo indicated that it protected mice against experimentally induced hemolytic infections and protected guinea pigs against induced gas-gangrene infections. Its action, similar in certain respects to that of penicillin, differs in that its bacterial activity appears to be directly proportional to its concentration, and its action is not inhibited by the organisms that produce penicillinase. Meleney observed that many cocci are susceptible to both penicillin and bacitracin. He also observed that many strains are resistant to penicillin but susceptible to bacitracin and that fewer are susceptible to penicillin and resistant to bacitracin. Hence, it is effective against a wider spectrum of pyogenic organisms in topical therapy and frequently succeeds when penicillin does not. This conclusion was again apparent in the effective response to bacitracin ointment of 90 per cent of the cases of infectious eczematoid dermatitis and contact dermatitis with secondary infection that were examined in this present series. All were industrial cases; many had been previously treated by other preparations, with poor response. Cultures taken from a large percentage of these cases usually proved to be streptococcus, *Staphylococcus aureus* or both and were highly susceptible to bacitracin. Without exception these cases responded rapidly and without recurrence. Similar response in skin pyodermas has been reported by Miller and associates,[2] and by Derzavis and associates.[3]

Tested in vitro by dissolution in Sabouroud's media to make a 1/500 dilution, bacitracin supported the growth of all superficial dermatophytes and deep fungi tested: *Microsporum audouini, M. fulvum, M. lanosum, Epidermophyton inguinale, Trichophyton gypseum, T. purpureum, T. schoenleini, T. sulfureum* and *T. violaceum*. It also appears definitely to accelerate the growth of yeasts, including *Candida albicans* and *Cryptococcus hominis*, and supports the growth of actinomyces.

Antibiotics and the sulfonamides have precipitated a mild revolution in the treatment of acute external otitis and chronic suppurative otitis, ever since the comprehensive report of Senturia,[4] who first recognized their bacterial (principally gram-negative) rather than fungous origin. These drugs have materially reduced the incidence of therapeutic failure.

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Their consistent use in aural therapy, however, has been frequently contraindicated because of the accompanying incidence of allergenic reactions.

During the treatment of the external otitis cases in this series, — all of which cleared without recurrence, — the nonallergenic properties of bacitracin were specifically illustrated in the case of a forty-five-year-old schoolteacher who had had a thick purulent discharge from both ears of five months' duration. This condition had not responded to considerable previous treatment. During the initial office examination both ear lobes presented a local sensitization dermatitis with marked edema, erythema and vesicles extending out to the adjacent skin of the cheek and neck. The ear lobes were treated conservatively with Burow's-solution compresses and zinc lotion. The dermatitis cleared within six days. Bacitracin aqueous drops were then used in the external ear canal; on the patient's next office visit, twenty-four hours later, the discharge had cleared. Bacitracin drops were used prophylactically, daily for fourteen days. When last examined, the patient had been symptom-free for six months.

Hitherto resistant pyogenic infections, such as impetigo rodens, which is relatively rare, responded rapidly and effectively to the ointment. Two of these scalp cases were of three years' duration. Since bacitracin must come in close contact with the invading organism to be wholly effective, crusts on the scalp were thoroughly removed with a bland soap-and-water scrub prior to each application of the ointment. There has been no recurrence in either of these two cases, both of which cleared completely in two weeks. The importance of bacitracin's direct contact with the invading organism has been stressed by Miller[5] and Blattner.[6]

Wet bacitracin compresses were efficient in the clearing of secondary infections, including those associated with old varicose ulcers. Because of its bactericidal effect, bacitracin ointment became the treatment of choice for dressings following all minor office electrosurgical and operative procedures such as the removal of keratoses, epitheliomas and warts. Secondary infection occurring after the removal of subungual warts has to date been completely eliminated by the use of bacitracin dressings.

Case Reports

Case 12. A 66-year-old man presented a deep ischiorectal abscess that had been incised six months previously and subsequently cauterized each week with silver nitrate. The incision was 12.5 cm. long and 2 cm. deep. The site had shown marked secondary infection for four months. Bacitracin compresses in a 1/500 solution were applied for twenty minutes three times daily during the following month. These were later applied only once daily, supplemented by boric-acid compresses twice daily. Healing commenced with the original application of bacitracin. The site cleared uneventfully in three months.

Case 36. A 10-year-old boy presented a severe extensive impetigo of three months' duration that covered both buttocks. The mother said that many ointments had been applied, with negligible response. All crusts were removed with soap and water; bacitracin ointment was applied. The mother continued this treatment five times each day, and the condition completely healed in two weeks.

Case 1. An 11-year-old girl presented a severe crusting of the entire scalp and upper third of the forehead, with some hair loss. The condition was of three years' duration, and the child had received considerable previous treatment. Crusts were removed with soap and water, and treatment continued at home as in the preceding case. The condition cleared in two weeks without recurrence.

Case 83. An 8-year-old boy presented a 3-mm. plaque of dry scaly dermatitis on the left upper eyelid that extended into the adjoining eyebrow, with complete hair loss in the involved portion. Treatment followed since the onset of the condition three weeks before had been ineffective. Bacitracin ointment completely cleared the impetigo in two days without recurrence.

Case 67. A 35-year-old man presented an extensive superficial infection in the hair follicles on both sides of the neck of four weeks' duration. Bacitracin ointment applied three times daily completely cleared the infection in six days.

Case 62. A 39-year-old shoe-worker, accustomed to sitting on a hard round-topped stool at his workbench for long periods of time, presented a six-year history of multiple recurrent boils. X-ray and various types of therapy had been ineffective. Bacitracin ointment applied for two months considerably reduced the incidence, and the condition showed marked improvement after the first week of treatment.

Case 78. A severe secondary infection in a varicose ulcer of three years' duration showed marked improvement after the application of bacitracin compresses for one week. This preliminary treatment has been administered successfully in all secondary ulcer infections prior to institution of conservative treatment of the ulcer.

Case 40. A 17-year-old boy presented a severe pustular acne of two years' duration that covered the forehead, cheeks and chin with multiple small and large pustules. Bacitracin compresses were applied for twenty minutes three times daily for three days, with marked reduction in the number of pustules and in the secondary infection and with marked improvement in the appearance of the acne.

Case 8. A 19-year-old girl, with a history of previous extensive treatment for four months, presented a marked pustular dermatitis plaque on the left sole measuring 10 cm. in diameter. For two weeks bacitracin ointment was applied three times daily after soap-and-water cleansing. At the end of this time the area had completely cleared. The condition has not recurred.

Case 18. A 38-year-old woman operated a marking machine that tagged merchandise for display in a large department store. In January, 1950, she pricked her left index finger with a wire sleeve ticket and immediately reported to the store clinic for treatment. A rash appeared at the site of the initial prick and gradually spread locally on the finger. Eight months later a similar rash appeared on the right little finger, right ring finger and right index finger. For nine months all treatment at the clinic had proved ineffective. Bacitracin ointment applied daily, preceded before each application by cleansing with soap and water, completely cleared the condition in one week.

Case 35. A 46-year-old man presented a pustular infection involving the distal third of the right index finger, accompanied by considerable dystrophy of the nail. The dermatitis had been entirely unresponsive to treatment for the previous four months. Bacitracin ointment completely cleared the condition in one week.

Case 15. A 35-year-old dishwasher presented a contact dermatitis of the hands from constant immersion in soap and water. There was also an extensive erythematous vesiculopustular dermatitis. Bacitracin ointment and boric com-

presses were applied for twenty minutes, three times daily, for one week, at which time the pustular element had entirely cleared, leaving the residual contact dermatitis.

CASE 3. A 48-year-old man had received extensive treatment for eight weeks of a sycosis vulgaris of the upper lip; treatment was ineffective. Soap and water to remove the crusting, followed by bacitracin ointment five times daily for two weeks, completely cleared the site of any evidence of pyogenic infection. There has been no recurrence.

CASE 6. A 34-year-old woman with a psoriasis involving the scalp had acquired a secondary infection of two weeks' duration. Bacitracin ointment cleared the secondary infection in two weeks.

CASE 22. A 61-year-old man presented a deep buttock ulcer of five months' duration that numerous medicaments had failed to heal. Bacitracin compresses were applied three times daily. In seven weeks the area showed marked improvement and was granulating rapidly; it healed uneventfully.

TABLE 1. *Bacitracin Topical Therapy: Results in 83 Cases.*

CONDITION	CLASSIFIED CASES	CURED	MARKED IMPROVEMENT	IMPROVED	FAILED	MINIMUM AND MAXIMUM NO. OF DAYS REQUIRED FOR CURE	AVERAGE NO. OF DAYS REQUIRED FOR CURE
Impetigo	12	12	—	—	—	4–10	7
Impetigo rodens	4	4	—	—	—	14–21	17
Furfuraceous impetigo	1	1	—	—	—	7	—
External otitis	5	5	—	—	—	7–21	9
Pustular acne (secondary infection)	2	—	2	—	—	6–6	—
Cystic pustular acne (secondary infection)	1	—	1	—	—	3	—
Pyoderma	12	6	4	1	1	7–14	12
Sycosis vulgaris	4	2	2	—	—	6–14	6
Folliculitis	6	5	—	—	1	6–14	11
Dermatitis	—	—	—	—	—	—	—
Dermatitis venenata with secondary infection	4	3	—	1	—	7–14	—
Infectious eczematoid dermatitis	19	7	12	—	—	3–14	7
Acrodermatitis continuë	1	1	—	—	—	7	—
Seborrheic dermatitis	4	—	1	3	—	7–14	—
Ischiorectal abscess	1	1	—	—	—	90	—
Recurrent boils	1	1	—	—	—	56	—
Secondary infection (psoriasis)	1	1	—	—	—	14	—
Ulcer (buttock)	1	1	—	—	—	49	—
Secondary infections (varicose and traumatic ulcers)	4	1	3	—	—	4–7	—
Totals	83	51	25	5	2	—	—
Percentage of totals		61.5	30.1	6.0	2.4		

SUMMARY AND CONCLUSIONS

Seventy-five patients with superficial pyodermas; 4 cases of secondary infections associated with varicose and traumatic ulcers; 1 ischiorectal abscess; 1 case of recurrent boils; 1 ulcer of the buttock; and 1 secondary scalp infection associated with psoriasis received topical therapy, — either with an ointment consisting of 500 units of bacitracin per gm. of petrolatum or with wet dressings of a solution containing 500 units of bacitracin per cc.

Forty-six cases in the first group completely cleared in from three days to three weeks without recurrence; 22 additional cases showed marked improvement; 5 improved and 2 did not respond to treatment. The deep ischiorectal abscess, buttock ulcer, secondary infection (scalp) and recurrent boils healed uneventfully in from three weeks to three months.

Secondary infections of old ulcers presented marked improvement in from four to seven days. Secondary infections associated with acne or psoriasis either cleared completely or showed marked improvement in from three to seven days.

The response of hitherto strongly resistant pathogenic infections was impressive, as observed in 1 case of dermatitis continuë that cleared in seven days and in 4 cases of impetigo rodens, 2 of which had been treated ineffectively for three years. Both these latter cases healed without recurrence in two weeks.

During the course of this study, bacitracin became the dressing of choice for all minor office electrosurgery and operative procedures such as moles, skin cancers, warts and so forth.

Ninety per cent of the cases of infectious eczematoid dermatitis and contact dermatitis with secondary infections were industrial cases. Many of these cases had been treated previously at various industrial clinics without apparent benefit. The action of bacitracin in these cases was rapid and effective.

The wide variety of infections presented by this entire group of 83 cases indicates that the therapeutic value of bacitracin is applicable in topical therapy to all pyogenic skin disorders caused by the streptodermas and staphylodermas.

Clinically, bacitracin is one of the most efficient bactericides that have been introduced into dermatologic practice. In treatment, it has materially reduced the time element (important in the industrial field). Moreover, since its allergic incidence is extremely low, the combination of a superior bactericide with a low sensitization index indicates that this compound is an excellent agent for the administration of topical therapy, — probably the most effective now available.

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References

1. Johnson, B. A., Anker, H., and Meleney, F. L. Bacitracin: new antibiotic produced by a member of the *B. subtilis* group. *Science* **102**:376, 1945.
2. Miller, J. L., Slatkin, M. H., and Johnson, B.A. Evaluation of bacitracin in local treatment of pyogenic infections. *Arch. Dermat. & Syph.* **60**:106-120, 1949.
3. Derzavis, J. L., Rice, J. S., and Leland, L. S. Topical bacitracin therapy of pyogenic dermatoses: clinical report. *J. A. M. A.* **141**: 191, 1949.
4. Senturia, B. H. Etiology of external otitis. *Laryngoscope* **55**:277-293, 1945.
5. Miller, J. L. Treatment of impetigo. *Postgrad. Med.* **6**:318-320, 1949.
6. Blattner, R. J. Bacitracin in local treatment of pyogenic infections. *J. Pediat.* **35**:790, 1949.

THE CUTANEOUS TOXICITY AND THERAPEUTIC EFFECTIVENESS OF PENICILLIN O*

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THE incidence of cutaneous reactions during penicillin therapy has been substantially reduced since a pure crystalline form of this drug has come into general use.[1] In certain patients, however, crystalline penicillin G must be used with caution or abandoned entirely because of the appearance of unpleasant or even hazardous reactions.[2-6] Although newer antibiotics are available, penicillin remains the treatment of choice frequently enough to warrant search for a less allergenic preparation.

In the study of the biosynthesis of penicillin G many different penicillins have been produced by altering the composition of the culture media.[7, 8] Most of these are of little clinical importance, but one, designated as penicillin O, due to its slight onion-like odor, offered promise because of its antibiotic potency and its failure to cause reactions in 57 patients known to be sensitive to penicillin G.[9] It differs from penicillin G (benzyl penicillin) in the presence of an allylmercaptomethyl group on the basic penicillin structure.

The present study was carried out to test the allergenic properties of penicillin O, to define the tolerance to penicillin O of patients known to be sensitive to penicillin G and to gain further knowledge of the therapeutic effectiveness of penicillin O.

Materials and Methods

Fifty-two hospitalized patients, consisting of 26 men and 26 women, were given penicillin O as a therapeutic or prophylactic measure. The patients were divided into 4 groups as follows: those who had shown sensitivity to penicillin on a previous occasion, those who had not received penicillin previously, those who had received penicillin on a previous occasion without manifesting sensitivity to it and those in whom the previous administration of penicillin could not be established with certainty. Throughout their hospital stay all patients were seen at frequent intervals by one observer.

Crystalline penicillin O potassium (Cer-o-cillin)§ of a single lot number was used throughout the study; physiologic saline solution was used as the diluent. Except in 2 patients who received the drug by aerosol inhalation, the drug was administered by intermittent intramuscular injection in doses ranging from 200,000 to 2,400,000 units daily. Total doses ranged from 300,000 to 32,840,000 units. Intrathecal injections were employed in conjunction with intramuscular injections in 1 patient. Therapy was continued for at least five days unless a sensitivity reaction occurred.

In 3 of the 5 patients whose histories indicated a previous penicillin reaction, intradermal tests were performed, using 200 to 500 units of crystalline penicillin G in 0.1 ml. of physiologic saline solution in one forearm and a similar quantity of penicillin O in the other. No reaction occurred at either skin-test site within twenty-four hours, and treatment with penicillin O was begun. This procedure was omitted in 2 patients who were in urgent need of therapy at the time when they were first seen.

Results

Of the 52 patients treated with penicillin O, 4 (7.7 per cent), all men, developed cutaneous reactions. The manifestations in 3 patients consisted of maculopapular eruptions over the upper thighs, buttocks, trunk and arms and, in the fourth patient, of facial and periorbital edema and a generalized maculopapular rash. Table 1 shows the relation between these reactions and the presence or absence of a history of previous exposure or sensitivity to penicillin G. In the group of 5 patients who had histories of skin eruptions attributed to penicillin, 3 had no reaction when penicillin O was administered, whereas 2 showed intolerance to both types of penicillin. The interval between the appearance of cutaneous sensitivity to penicillin G or to the early less pure preparation of penicillin and the administration of penicillin O was one day, one year and three years, respectively, in the 3 patients who tolerated penicillin O without reaction and one day and five years, respectively, in the 2 patients who manifested sensitivity to both types of penicillin. The daily doses of penicillin O

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ranged from 200,000 to 600,000 units, and the total doses ranged from 650,000 to 13,600,000 units in the 3 patients who tolerated penicillin O without reaction. The total doses of penicillin O were 300,000 units in a twelve-hour period and 1,700,000 units in a three-day period in the 2 patients in this group who developed cutaneous sensitivity to penicillin O.

TABLE 1. *The Occurrence of Cutaneous Reactions to Penicillin O in 52 Patients.*

History of Previous Administration or Reaction to Penicillin	Patients Treated with Penicillin O	
	no.	no. of drug reactions
Previous reaction	5	2
No previous administration	4	2
Previous administration without reaction	24	0
Previous administration unknown	19	0
Totals	52	4

There were 4 patients who had not received penicillin in any form prior to their treatment with penicillin O. Two patients in this group developed skin eruptions attributed to penicillin O. The daily doses of penicillin O in these 2 patients were 200,000 units and 1,200,000 units, and their total doses were 1,150,000 units and 8,800,000 units, respectively. One of these patients was given penicillin G four days after the appearance of cutaneous sensitivity to penicillin O; the skin eruption promptly recurred. The 2 patients in this group who tolerated penicillin O without reaction were given daily doses of 400,000 units and 600,000 units and total doses of 2,300,000 units and 5,100,000 units, respectively.

No instances of sensitivity to penicillin O were encountered in the group of 24 patients who were known to have received penicillin previously without manifesting sensitivity to it or in the group of 19 patients in whom previous administration of penicillin could not definitely be established but in whom no sensitivity to penicillin was known to have occurred. Daily doses of penicillin O ranged from 200,000 to 2,400,000 units and the total doses ranged from 1,000,000 to 32,840,000 units in these 2 groups.

Six patients in the entire group gave histories of recurrent attacks of hay fever or of asthma. They had all received penicillin G on a previous occasion, and 1 had experienced a cutaneous eruption attributed to penicillin G. None of these patients reacted unfavorably to penicillin O.

Two patients received penicillin O by aerosol inhalation. Both had received penicillin G parenterally on a previous occasion, and 1 of them had manifested cutaneous sensitivity to penicillin G. Both tolerated penicillin O in aerosol without reaction.

The effect of treatment with penicillin O was evaluated in 28 proved or suspected bacterial infections. Nine patients with pneumococcal pneumonia were treated early in their illness, and all showed a rapid subsidence of fever. The temperature remained normal after forty-eight hours of therapy in 7 of these patients and after sixty hours of therapy in 2 patients. The leukocyte counts dropped to below 10,000 within six days in 8 of the 9 patients. The throat and sputum cultures were cleared of the infecting organism in 8 patients. The ninth patient made rapid clinical improvement but retained a Type 3 pneumococcus in his throat until the time of discharge from the hospital. Serial roentgenograms showed clearing of the pneumonic infiltrations in all cases.

Ten cases of pneumonia with normal bacterial flora in cultures of the sputum and throat on admission were suspected of being of bacterial etiology because of an abrupt onset, initial prostration, high fever and leukocytosis. The response following administration of penicillin O in these patients was less dramatic, but temperatures were normal within four days and leukocyte counts normal within eight days in all cases.

A patient who had been comatose for ten hours and was critically ill with a Type 3 pneumococcal meningitis arising from a middle-ear infection received on admission 20,000 units of penicillin O intrathecally and 200,000 units every two hours intramuscularly; 5 gm. of sodium sulfadiazine were given intravenously. Intrathecal injections of 10,000 units of penicillin O were given sixteen and seventy-two hours after entry. Pneumococci could no longer be demonstrated by smear or culture in the cerebrospinal fluid after sixteen hours of therapy. The patient regained consciousness in thirty hours, and the temperature was normal in sixty hours. Recovery was complete after twenty-one days of combined penicillin O and sulfadiazine treatment. The total dose of penicillin O was 32,840,000 units, and the total dose of sulfadiazine was 89.5 gm.

Three cases of acute tonsillitis due to Group A beta-hemolytic streptococci were treated with penicillin O within thirty-six hours of the onset of their symptoms. Two of these patients showed rapid clinical improvement with absence of beta-hemolytic streptococci from throat cultures after twenty-four hours, normal temperatures after thirty hours and return of leukocyte and differential counts to normal after forty-eight hours of treatment. The clinical response of the third patient was slower. Beta-hemolytic streptococci were present in cultures of his throat for forty-eight hours after treatment was begun, and his temperature was not consistently normal until five days of treatment were completed. The diagnosis of streptococcal infection in each of these 3 patients was confirmed by a rise in titer of antistreptolysin during convalescence. Two patients admitted in diabetic acidosis had abscesses of the upper thigh from which beta-hemolytic streptococci were cultured. Penicillin O combined with surgical drainage resulted in a normal temperature in four and five days, respectively. One

patient (Case 4) with a coagulase-positive *Staphylococcus aureus* bacteremia had a normal temperature and sterile blood culture within twelve hours of the initiation of treatment with penicillin O.

Case Reports

The case histories of those patients who developed hypersensitivity to penicillin O are presented briefly.

Case 1. A 79-year-old man was acutely ill with a bronchopneumonia of probable bacterial origin of four days' duration at the time of admission. There was no history of allergy or of previous penicillin therapy. Crystalline penicillin G in a dose of 100,000 units was given every four hours intramuscularly for seven days, after which the drug was discontinued because of the appearance of a nonpruritic maculopapular rash over the buttocks, back and arms. Pyrabenzamine, 50 mg. every four hours, was started and was continued during the subsequent week. No local reaction was observed to intradermal injections of 500 units of penicillin G or penicillin O. Twenty-four hours after penicillin G was discontinued penicillin O was begun in a dosage of 100,000 units every four hours. Thirty-six hours later the patient complained of itching, and the previous rash became intensely red and more widespread. The skin-test site for penicillin O showed marked erythema and induration at this time, whereas that for penicillin G showed no reaction. Penicillin O was stopped, and the rash subsided in four days. The characteristics of the skin eruptions and their temporal relation to the administration of penicillin G and penicillin O indicated that the penicillins, rather than any of the other drugs which the patient received (Demerol, chloral hydrate and Pyrabenzamine), were responsible for the skin eruptions.

Case 2. A 50-year-old man was admitted with an acute bronchiolitis and probable early pneumonia of undetermined cause. He gave a history of marked facial edema during penicillin therapy five years prior to admission. He was given 100,000 units of penicillin O and two hours later developed itching about the eyes. Six hours later facial and periorbital edema were present. Benadryl, 50 mg. every four hours, was begun and was continued for five days. Nevertheless, the patient developed a generalized pruritic, maculopapular eruption, which subsided in four days. The skin eruption was attributed to penicillin O because of its clinical characteristics and because the other drugs given prior to the appearance of the skin eruption, — Demerol and chloral hydrate, — were well tolerated subsequently.

Case 3. A 57-year-old man was admitted with a mild bronchopneumonia of undetermined etiology. He had had no previous penicillin therapy. He received 50,000 units of penicillin O every four hours for three and a half days, after which the drug was discontinued because of the appearance of a fine pruritic, scarlatiniform rash over the trunk and arms. The rash subsided rapidly. The only other medications had been a capsule containing aspirin, acetophenetidin and codeine, given thirty-six hours prior to the development of the rash, and six tablets of Priodax (beta [4-hydroxy-3, 5-diiodophenyl]-alpha-phenyl-proprionic acid), given three hours prior to the appearance of the rash. Patch tests with these substances and an intradermal skin test with 200 units of penicillin O were all negative. Clinically it was considered that penicillin O was the agent responsible for the rash, although a reaction to Priodax could not be excluded with certainty.

Case 4. A 75-year-old man was treated for bacterial endocarditis of two weeks' duration. Four blood cultures grew a hemolytic, coagulase-positive *Staphylococcus aureus* that was sensitive to 0.25 units of penicillin G per ml. and 0.03 units of penicillin O per ml.* The patient could not recall having previously received penicillin in any form. Penicillin O was given initially in doses of 100,000 units every three hours for four days; the interval between injections was then reduced to two hours. On the ninth day a confluent maculopapular rash appeared over the buttocks, chest and arms. Penicillin O was stopped and aureomycin was given for four and a half days, during which time the rash faded. Penicillin G was begun in small doses that were gradually increased to 25,000 units every six hours. After forty-eight hours the itching recurred and the rash reappeared. Penicillin G was stopped and aureomycin resumed. Aspirin, codeine and sodium pentobarbital had been given at various intervals prior to the occurrence of the initial skin eruption, but their administration had no temporal relation to the rash. Recurrence of the rash when penicillin G was given further identified the penicillins as the drugs responsible for the cutaneous manifestations in this patient.

*Sensitivity studies were performed by Dr. R. F. Parker.

Discussion

In this series of 52 patients treated with penicillin O, 4 developed cutaneous reactions. Two of the reactions occurred in patients who had not received penicillin in any form previously and 2 occurred in patients who had experienced untoward reactions during previous administration of penicillin G. Three patients in whom penicillin G had previously caused skin eruptions tolerated penicillin O without difficulty. One of these patients was given penicillin O within thirty-six hours of the time when his reaction to penicillin G was apparent. This experience differs from that of Volini and others,[9] who found that sensitization to penicillin O failed to develop in 57 consecutive patients known to have had a reaction to penicillin G one to two hundred days previously.

The results of the present study indicate that penicillin O is capable of producing toxic skin reactions not only in patients previously sensitive to penicillin G but *de novo* in patients who have not had prior penicillin reactions. Administration of penicillin O produced no untoward skin manifestations in 3 patients previously sensitive to penicillin G. It is possible that reactions would not have developed in this group even if penicillin G had been readministered. Skin tests in 2 of these 3 patients showed no reaction to either penicillin G or penicillin O. The results of this study do not permit any precise statement concerning the relative allergenic potency of penicillins G and O; contrary to previous reports, however, it is apparent that penicillin O is capable of producing allergic reactions.

In-vitro studies[10] have shown that penicillin O has essentially the same spectrum of antibiotic activity as penicillin G but that in some instances it may have only half the potency of penicillin G by the usual assay methods. The present study indicates the clinical effectiveness of penicillin O in the more common gram-positive coccal infections. In those cases in which a definite diagnosis was established, the response to treatment was clinically comparable to that seen in similar infections treated with penicillin G. The experience in a single case (Case 4) suggests that penicillin O may be the drug of choice in selected cases in which an organism is actually more sensitive to it than to penicillin G. Laboratory variation in this instance may account for the apparent greater sensitivity of the organism

to penicillin O, but the possibility that this was an actual difference cannot be excluded.

Summary

Penicillin O caused cutaneous reactions in 4 of 52 patients who received this drug. Two reactions occurred in patients who had shown prior sensitivity to penicillin G, and 2 occurred in patients who had no previous exposure to penicillin.

Penicillin O was tolerated without reaction by 3 patients in whom penicillin G had caused toxic skin eruptions.

Penicillin O was an effective antibiotic agent in a small series of patients with gram-positive coccal infections.

References

1. Lepper, M. H., et al. Studies on hypersensitivity to pegicillin. I. Incidence of reactions in 1303 patients. *J. Clin. Investigation* **28**: 826-831, 1949.
2. Wilensky, A. O. Fatal delayed anaphylactic shock after penicillin. *J. A. M. A.* **131**:1384, 1946.
3. Barksdale, E. E. Discussion of Morginson, W. J. Toxic reactions accompanying penicillin therapy. *J. A. M. A.* **132**:915-919, 1946.
4. Waldbott, G. L. Anaphylactic death from penicillin. *J. A. M. A.* **139**: 526, 1949.
5. Rabinovitch, J., and Snitkoff, M. C. Acute exfoliative dermatitis and death following penicillin therapy. *J. A. M. A.* **138**:496-498, 1948.
6. Berne, R. M. Unusual sensitivity reaction to penicillin: report of case with autopsy findings. *New Eng. J. Med.* **242**:814-817, 1950.
7. Behrens, O. K., et al. Biosynthesis of penicillins. I. Biological precursors for benzylpenicillin (penicillin G). *J. Biol. Chem.* **175**: 751-764, 1948; II. Utilization of deuterophenylacetyl-N^{15}-dl-valine in penicillin biosynthesis. *Ibid.* **175**:765-769, 1948; III. Preparation and evaluation of precursors for new penicillins. *Ibid.* **175**: 771-792, 1948; IV. New crystalline biosynthetic penicillins. *Ibid.* **175**:793-809, 1948.
8. Ford, J. H., Nelson, H. A., DeVries, W. H., and Hanson, R. Gamma-chlorocrotyl-mercaptoacetic acid and gamma-chlorocrotyl-mercapto-methyl penicillin. *J. Am. Chem. Soc.* **70**:3522, 1948.
9. Volini, I. F., Shlaes, W. H., and Felsenfeld, O. Use of penicillin O in patients hypersensitive to penicillin G. *J. A. M. A.* **143**:794-797, 1950.
10. Bliss, E. A., and Todd, H. P. Comparison of eight antibiotic agents, in vivo and in vitro. *J. Bact.* **58**:61-72, 1949.

MEDICAL PROGRESS

RADIOLOGY IN BONE PATHOLOGY*

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THE DISCOVERY of the roentgen ray gave tremendous impetus to the investigation and clarification of poorly or little understood disease entities and to the recognition of new ones. Of all the body structures the bones were the first to be extensively studied by this means. There has been an understandable lag, however, between the roentgenographic demonstration of bone abnormality and its clinical identification. Progress along these lines is dependent on the correlation of all branches of medicine, — clinical, laboratory, pathologic and radiologic. Recent years have witnessed the reassessment and reclassification of many disease processes. In the identification of any particular bone lesion certain innate difficulties confront both the radiologist and the pathologist.[1] Their two lines of approach are interdependent, and by the correlation of the two the discrepancy now at times apparent between radiologic and pathologic findings should steadily lessen.

The present review attempts a brief survey of the field since Mallory[2] reported in 1942 on certain aspects of bone pathology. The literature published during the past eight years is too voluminous for detailed coverage. Emphasis has been placed primarily on articles concerned with the correlation of radiologic and pathological examinations, certain newly established entities and improvements in roentgenographic methods for the better demonstration of bone lesions. For more complete study of this extensive subject, several excellent textbooks are recommended.[3-6]

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Pediatrics

In 1948 Caffey[7] said: "One of the great deficiencies in pediatric roentgenology has been and still is the lack of satisfactory standards for the normal structures at different ages and for the normal ranges of variation in both morphology and function. This deficiency is gradually being lessened by careful roentgen studies of large groups of normal infants and children in clinics devoted to normal child development." An accurate estimation of skeletal maturation in older children is to be found in the work of Todd.[8] Satisfactory standards for normal bone maturation in healthy living infants have been presented more recently by a number of investigators.[9-17]

The use of serial roentgenograms of the radius in the diagnosis and regulation of therapy in cases of congenital myxedema is described by Woolley and McCammon.[18] Standard lengths of radiuses in children up to two years of age are given, as well as a curve showing the normal growth rate of the radius.

Henderson and Sherman report the roentgenographic anatomy of the skull in newborn infants,[19]

basing their findings on examination of 100 healthy subjects.

Hypophosphatasia, a new developmental anomaly, is described by Rathbun.[20] This is apparently the first account of faulty bone development associated with absence of alkaline serum phosphatase. The patient, a poorly nourished infant with deformities of the wrists and bowing of the legs, died shortly after birth. X-ray examination revealed marked generalized skeletal decalcification, with deformities of the ribs and lack of normal calcium density at the metaphyseal ends of the long bones, simulating rickets. The epiphyses were not affected. Pathologic fractures were present. Although the kidneys contained numerous casts in the tubules no calcium or calcium phosphate was present. The vault of the skull showed a normal osteoid framework but no calcium deposits. This was regarded as an instance of primary failure by osteoblasts to produce alkaline phosphatase.

A congenital syndrome of mechanical origin has been reported by Caffey.[21] The prenatal bowing and thickening of tubular bones with multiple cutaneous dimples in the arms and legs are, he believes, caused by mechanical intrauterine pressure and pressure atrophy of the fetal skin. A somewhat similar appearance may be caused by rickets and Blount's tibial osteochondrosis. Many of the bony deformities disappear with age, — especially those of the upper extremities, — but some may persist during the third year of life. This condition is similar to the entity described by Heyman and Herndon[22] and by Barber[23] in which congenital posterior angulation at the junction of the middle and lower thirds of the diaphysis of the tibia takes place. The bone otherwise appears to be of normal structure, and there is no disturbance in the lower tibial epiphysis. Good prognosis, with straightening of the tibia, follows conservative treatment.

Diastematomyelia, a condition that consists of an embryologic defect of the neural axis and spinal column with a sagittal division of a segment of the cord or cauda, is discussed by Neuhauser, Wittenborg and Dehlinger.[24] This sagittal division occurs most commonly in the lumbar area, but cases have been reported in which it extended to the seventh thoracic vertebra. The cord or cauda equina is transfixed by an osseous or fibrocartilaginous septum, which takes origin from the anterior portion of the vertebral body and is attached posteriorly to the dura. Roentgenologic examination shows widening of the neural canal, abnormal development of the vertebras and, at times, a midline osseous spicule. In the presence of these findings the diagnosis can be made without further procedure. If, however, a fibrous or cartilaginous septum is present the diagnosis must be confirmed by myelography. The recognition of this condition is particularly important, as it may be remedied by surgical treatment. Because of the transfixing spicule or septum the cord is prevented from making its normal ascent; consequently, Arnold–Chiari malformations and hydrocephalus may be associated abnormalities. The clinical signs and symptoms are significant; the patient may show evidence of impaired innervation to the lower extremities, such as clubfoot or disturbance of sphincteric control. A defect of the skin suggesting spina bifida, such as excessive hair, skin dimple or nevus, may be noted; rarely there may be a meningocele.

Dysplasia epiphysialis punctata or chondrodystrophia calcificans congenita is a rare disease characterized by the presence of numerous discrete centers of unusual density in many of the epiphyses. Borovsky and Arendt[25] report a case of this condition, which apparently exhibits no hereditary or familial influence and affects females twice as often as males. Fairbank,[26] in reviewing the literature, found that of the 16 published cases the disease was recognized in 14 before the age of nine months, suggesting that dysplasia began in fetal life. The affected epiphyses are enlarged and dwarfing is usually present, with limitation of motion and varying degrees of contracture. Other features of the disease are thickening of the skin, broadening of the nose, large nostrils, bilateral cataracts, dulling of the intellect and weakness. The epiphyses show a diffuse stippling, as if there were multiple centers; the centers may become smaller and fewer in number or may fuse. The spotted epiphyses appear at an earlier date than do normal ossification centers. The follow-up study of these patients was incomplete; half were known to have died; in one instance examination at the end of a nine-year period showed definite improvement in the appearance of the epiphyses, with fusion of the multiple centers. It is noted that the discrete stippling is distinct from the mottling and epiphyseal irregularity seen in cretins. Neuhauser[27] has noted the occurrence of calcification of the cartilaginous rings of the trachea and bronchi. The resultant stiffening of the rings interferes with normal exchange of air in the lungs so that infection is prone to occur with subsequent death.

Neuhauser and his colleagues[28] present four cases, three of them in girls, of progressive diaphyseal dysplasia, another extremely rare entity, previously described in 1929 by Engleman. The syndrome is characterized by progressive symmetrical alteration in the diaphyses of the long bones, retardation of growth, both in height and weight, and muscular weakness. X-ray examination shows symmetrical distribution, with fusiform enlargement of the diaphyses of the long bones; the epiphyses and metaphyses are normal. Thickening of the cortex by endosteal and periosteal accretion of mottled new bone without recognizable trabecular pattern is manifest. Skull involvement when present has been confined to the base, which has shown amorphous increased thickness and density re-

sembling changes occurring in fibrous dysplasia. As a rule the hands, feet, ribs, spine and pelvis are not involved in the process. The lesion is sharply demarcated in the shaft and progresses along the long axis of the bone, both proximally and distally, with gradual alteration of previously normal bone. The extremity is relatively elongated compared with the size of the child. This condition resembles Paget's disease in that there is progressive change in the cortical architecture; it differs from Paget's disease in its lack of coarse accentuation of the trabecular pattern, the new cortical bone being of amorphous density without any pattern. The alkaline phosphatase is not affected, and the microscopical characteristics of Paget's disease are absent. The lesion may be distinguished from infantile cortical hyperostosis by the age incidence, distribution and symmetry of involvement and its progressive nature. Although skeletal changes are the most obvious features, associated abnormalities suggest a widespread disease process.

A somewhat similar case is reported by Sear,[29] and Ribbing describes four siblings with like abnormalities.[30] In the latter report, however, the condition was familial, which was not true in Neuhauser's cases.

In 1945 Caffey and Silverman[31] reported on the principal features of a syndrome, infantile cortical hyperostosis, that has its onset in the early part of the first year of life. A year later the findings in 6 additional cases[32] were published. The condition is characterized by tender swellings in one or more sites, — the face, jaws, scapular regions and extremities. Multiple scattered hyperostoses are demonstrated radiographically in bones adjacent to the soft-tissue swellings, as well as in other bones over which the soft tissue appears to be normal. Despite these signs of disease the patients exhibit in all phases of the illness a striking lack of constitutional and systemic manifestations. The cortical thickening tends to diminish and disappear after several months, although occasionally swelling of the face may persist for two or three years.

Smyth[33] reported in 1946 on what he called a "new syndrome," which appears to have been the same entity described by Caffey. More recently Sherman and Hellyer[34] have reviewed the literature and added five cases to the 27 previously published. In the entire group, — 15 males and 12 females, — all parts of the skeleton except the phalanges, the small bones of the carpus and tarsus, the vertebras and the pelvis have been involved. The etiology of the process is still unknown. Although the number of reported cases is relatively small, the actual incidence is probably much greater.

Caffey has described 6 infants in whom multiple fractures in long bones were discovered in the presence of chronic subdural hematoma.[35] In no case was there a history of injury to which the skeletal lesion could reasonably be attributed, and in none was there evidence of generalized or localized skeletal disease that would predispose to a pathologic fracture. Several of the fractures occurred after the first clinical evidence of subdural hematoma, but nothing in the history suggested that convulsive seizures or head injury could have been responsible for the fractures; their cause remains obscure. It is concluded that in the presence of unexplained fracture in the long bones of infants investigation with a view to possible subdural hematoma is warranted. Conversely, if subdural hematoma is known to be present, routine examination of the long bones should be made in order to rule out the presence of clinically silent fractures.

Because of the common misinterpretation of double contours of the long bones and of cupping and spur formation at the ends of bones at the epiphyseal plate in infants, Glaser[36] investigated premature infants by means of serial studies over an eight-month period. The double contour frequently seen along the shaft of the bone was shown to result from the presence of normal bony ridges that were projected adjacent to the cortex, thus simulating the appearance of periosteal reaction. Similarly, cupping may be simulated at the distal ends of bones, particularly the tibia and fibula, by projection of these structures rather than actual morphologic disturbance. Re-examination with careful technical details can readily clarify such clinical misinterpretations.

The importance of close observation of *both* hips when treatment for congenital dislocation by means of abduction and external rotation is being carried out is pointed out by Tucker.[37] In this position aseptic necrosis of the sound hip may result because of impairment of the vascular supply to the femoral head by pressure upon the acetabular lip.

Pseudohypoparathyroidism, described by Albright and his co-workers[38] in 1942, has the same symptoms and chemical and clinical findings as hypoparathyroidism. The former condition, however, results not from a lack of parathyroid hormone but from an inability to respond to it. In addition, associated developmental abnormalities further distinguish it from true hypoparathyroidism.[5] In both conditions the physical appearance of the patients is the same; their faces are usually round and their stature short and thickset. The most striking feature is a tendency to brachydactylia, due chiefly to shortening of the metacarpal and metatarsal bones. Other congenital abnormalities associated with pseudohypoparathyroidism (early union of epiphyses around the elbow, bowing of the radius, and exostoses) suggest that the disease is related to dyschondroplasia. In addition to the skeletal abnormalities, soft-tissue calcifications may occur in the extremities and in the basal ganglia of the cranium. The shortening of the metacarpal

and metatarsal bones should not be confused with familial brachydactylia, which may be present as a predominant Mendelian character and is not necessarily associated with pseudohypoparathyroidism.[39]

Infections

Osteomyelitis

Acute osteomyelitis. One of the newer observations is that osteomyelitis of the acute fulminating type is becoming a disease of the past. This fact seems to be due to the use of antibiotics. It is apparent to the radiologist as well as to the clinician that there are fewer severe acute infections, including postoperative complications, than in the preantibiotic days. Nevertheless, it is imperative that certain radiologic changes be recognized when serious infections do occur.

In acute osteomyelitis, roentgen changes in bones are not evident until ten to fourteen days after the onset of illness. This delay in diagnosis has been reduced by the results of soft-tissue studies[40] that have shown that during this phase of the disease changes in these structures may be demonstrated radiographically, thus providing an earlier diagnosis. Loss of intermuscular planes and loss of the fat shadow beneath the subfascial planes may appear as early as twenty-four hours after the first clinical symptoms. As bone abnormalities manifest themselves, those in the soft tissues regress, which fact suggests that the soft-tissue changes are due to increased intraosseous blood-vessel and lymphatic pressure. Of first importance in differential diagnosis is the fact that the soft-tissue edema is apparent throughout the length of the bone in acute osteomyelitis whereas in tumor and trauma it is usually confined to localized areas.

McAdam[41] emphasizes the profound changes that have taken place in osteomyelitic reactions under penicillin therapy; others note the lessened severity of the residual bone changes following subsidence of the acute disease.[42, 43] Altemeier and Reinecke[42] divide their 52 cases of acute hematogenous osteomyelitis into four groups: Group 1, cases recognized and treated within one to three days after onset, with no or minimal bone changes; Group 2, those with duration of disease of more than one week with minor bone changes and occasional sequestration; and Group 3 and Group 4, those with severe and fulminating infections, which in preantibiotic days would probably have terminated fatally and in which today the patients are less severely ill and in many instances recover. In the last two groups, also, the bone changes are less marked and more readily restored to normal than formerly. The roentgenographic evidence of repair appears at a much later date than do the clinical signs of improvement.[43]

It has been reported by Hutter[44] that acute osteomyelitis may occur in the newborn, usually during septicemia. The area about the hip seems to be most frequently involved. X-ray examination commonly shows widening of the joint space with apparent lateral displacement of the femoral head. This can be distinguished from congenital dislocation by the preservation of the normal arch of the acetabulum and by the soft-tissue swelling noted in osteomyelitis with the usual later demonstration of periosteal elevation and bone destruction.

Osteomyelitis is a complication that not uncommonly follows marrow infusions in infants. Two patients who had received continuous intraosseous infusions with resultant osteomyelitis are described by Texter, Irwin and Kaump[45]; both infants responded to penicillin therapy. The same authors reviewed 19 previously published cases. They found that in patients receiving continuous infusions and in those to whom hypertonic solutions were administered the incidence of osteomyelitis rose from 6 to 13 per cent.

Common causes of *chronic osteomyelitis* are tuberculosis, coccidioidomycosis and other fungous diseases.[46-49] The roentgenographic aspects of these conditions have been extensively described. Less familiar infections causing similar bone changes are disseminated granuloma inguinale,[50] echinococcic involvement,[51] torulosis[52] and leprosy.[53] Certain sporadic cases of leprosy may appear in temperate zones when transmitted from endemic areas by members of the armed forces or their families. The radiologic appearance of bone changes is no different from that previously known.

Infections of Unknown Etiology

Certain idiopathic lesions of the feet may be of infectious rather than neuropathic origin, according to Hodgson and his colleagues.[54] They are characterized by absorption of bone, decrease in the caliber of bone and "pencil-point" deformity of the metatarsals. In a study of 61 such cases only one common factor was found, — infection in adjacent soft tissue. The authors believe that infection is responsible for these changes, which were previously attributed to neuropathy.

Cooper and others[55] report an instance of familial osseous atrophy, demonstrated roentgenographically. The bone abnormalities seem to have been similar to those reported by Hodgson; the familial incidence is interesting.

Tumors

Benign Tumors

Giant-cell tumors (*osteoclastoma*). Although this group of lesions is the subject of considerable controversy, reclassification of its various components represents one of the advances in the diagnosis of bone disease.[56] Andersen[57] and Lichtenstein[58] discuss the present discrepancies of classification, theoretical etiology and methods of treatment;

both clearly indicate the need of biopsy to obtain positive diagnosis as well as to differentiate benign and malignant varieties. Brailsford,[59] on the other hand, believes that biopsy not only reveals nothing beyond the diagnosis already made by x-ray examination but may actually disseminate tumor cells, weaken bone or cause risk to the patient. He contends further that surgical trauma may incite malignant change and that x-ray therapy, which produces an apparent osteolysis, should be used judiciously and only after the institution of careful protective measures. Brailsford's views have not been received with enthusiasm in this country.

Jaffe[60] excludes all the so-called variants because they have little in common clinically or anatomically with genuine giant-cell tumor. In a study of selected lesions of this type it is found to be a relatively uncommon, highly distinctive tumor, which, far from being consistently benign, frequently shows aggressive characteristics. It is rarely seen before the age of 20; it usually occurs in the end of a long bone, almost always involving the epiphysis, and seldom produces the typical "soap-bubble" appearance. Jaffe grades giant-cell tumors by their increasing number of stromal cells. The "plumping up" of these cells, particularly of their nuclei, the mitotic division of many and the presence of one or more very large nuclei are important factors in gradation. He considers either a Grade II or a Grade III lesion serious, not only requiring amputation but often proving fatal.

In brief, it may be stated that giant-cell tumor is a true tumor, sometimes malignant; it occurs most often between the ages of 20 and 30 years; it usually extends to the end of a long bone; it may present as an area of expansile destruction or as an expansile "soap-bubble" type of lesion; it is best treated surgically, but if this is not feasible roentgen therapy may be of value.[58] If irradiation of a giant-cell tumor is undertaken the radiologist should be aware of the typical so-called paradoxical reaction that results from treatment. For perhaps two to four months after treatment the lesion may appear to be progressing; later this reaction subsides and healing becomes evident.

A "benign" *chondroblastoma*[62, 63] has a radiographic appearance that is very similar to that of a giant-cell tumor. Another process that may be confused with giant-cell tumor is *aneurysmal bone cyst*,[64, 65] which is most often seen in the age group between 10 and 20, rarely in young adults. It may be located in vertebras, flat bones or long bones. The patient may experience pain and note the presence of a "lump." On x-ray examination this cyst presents as a "ballooned-out" eccentric lesion involving only a portion of the bone width. When it is located in the shaft of a long bone it has a trabeculated ("soap-bubble") appearance, and differential diagnosis is difficult. Pathological examination has shown that the bone is replaced by vascular fibrous tissue; blood-filled channels are present in supporting connective tissue, in which there is hemorrhage and giant-cell and new-bone formation. It is reported as benign.

Jaffe and Lichtenstein[66] have described 8 cases of chondromyxoid fibroma of bone, which they believe is a benign entity likely to be mistaken for chondrosarcoma. The patient's complaints are minimal; pain, usually present, is intermittent and does not necessitate hospitalization as a rule until some months after onset. When the lesion is found in the long bones, it is in the metaphyseal end, usually without involvement of the epiphysis; even in the small bones it tends to be eccentric, — ovoid in shape, with its long axis in the long axis of the affected bone. It is lytic, with a distinct adjacent zone of sclerosis, which may be grooved. Coarse trabeculations may be associated with a thin expanded shell of bone, which is often difficult to recognize. Although the authors claim that this lesion is easily recognized, its appearance on x-ray films, so like that of a giant-cell tumor in the metaphyseal portion of bone, may be difficult to distinguish from chondrosarcoma or fibrosarcoma.

A similar roentgenographic appearance has been described by Longstreth,[67] in the case of a myxochondrosarcoma of the talus. The patient, a 62-year-old man, developed a mass about the ankle after a minor injury, with limited motion of the joint. X-ray examination demonstrated destruction of the superior margin of the talus, with soft-tissue involvement. Although the histologic report on the original biopsy was chondrosarcoma, at amputation a year later the diagnosis was myxochondrosarcoma. The patient subsequently developed lung metastases and died.

Osteoid osteoma. Although it was described in 1935, it is only in recent years that this lesion has been established as a common entity. Jaffe[68] and his associates have been the leaders in promoting this process to the position of a peculiar benign tumor; others contend that it is a form of chronic sclerosing osteomyelitis. Whether it be tumor or osteomyelitis, it is relatively common, occurring usually in young persons between the ages of 10 and 30. Pain and local tenderness are its chief clinical features; considerable sclerosis of bone, with a central nidus, is the outstanding characteristic as seen by x-ray. At first the nidus may be very dense, surrounded by local rarefaction that is succeeded by an area of sclerotic bone. The nidus later loses its density, and a central area of rarefaction is found within a larger area of sclerotic bone. Surgical excision, if the nidus can be removed, affords relief.

Moberg,[69] in a study of the natural course of an osteoid osteoma without surgical intervention, offers some interesting observations on the character of this condition. He describes the course of the disease in two *histologically unproved* cases that

had the typical roentgenographic appearance and later spontaneous healing.

Malignant Tumors

Ewing's tumor. This queer tumor is well known yet still presents unusual manifestations. Lichtenstein and Jaffe[70] report on 17 cases, in 5 of which complete autopsies were obtained. The majority of the tumors were found in patients between 12 and 19 years of age.

Out of 192 primary bone tumors, McSwain and his colleagues[71] report 20 as Ewing tumors. Of the 20, only 3 lived five years or more without recurrence; 1 survived fourteen years before dying of metastatic disease. These authors found a 9 per cent five-year survival in an analysis of 565 cases of Ewing's tumor, collected from previously published reports.

Although surgery in the treatment of this tumor may rarely be successful, x-ray therapy is the treatment of choice in most instances.[72]

Osteogenic sarcoma. Jaffe[60] believes that this group of tumors should be divided into the recognized components, such as true osteogenic sarcoma, fibrosarcoma and chondrosarcoma. Many others, however, consider that for the purposes of follow-up study all these forms should be classed under one broad general heading. As classified by Jaffe, osteogenic sarcoma is the most common malignant tumor of bone. Approximately one half of the bone tumors, as well as of the soft-tissue extensions, are ossified and eburnated to a considerable degree, the other half to a lesser extent. Fibrosarcoma may present as an area of destruction in cortical bone with soft-tissue extension, which, however, is not ossified. Chondrosarcoma, frequently beginning as a central lesion, is slow-growing; whether central or otherwise, it tends to retain its original growth tendency. In the osteogenic group as a whole, there is usually evidence of a lesion within the bone, which may be either destructive or sclerotic. A periosteal cuff with an associated soft-tissue mass is characteristic. X-ray differentiation of the various types is difficult or impossible. Clinically, osteogenic sarcoma and fibrosarcoma usually occur in patients between the ages of 10 and 25, whereas chondrosarcoma is found more often in those between 25 and 50. Biopsy is the only means of securing a positive diagnosis.

Prevo[73] reports that 0.8 per cent of all orthopedic patients seen in his clinic were suffering from some form of bone tumor, either benign or malignant. He points out that in Ewing's tumor a five-year freedom from metastasis does not exclude the possibility of its later recurrence whereas in other tumors five-year "cures" are much more indicative of lasting favorable results.

Coley and Harrold[74] found 59 cases of five-year survival in a group of 262 determinate cases of osteogenic sarcoma. They agree with Jaffe that the pathological classification should be broken down into subdivisions, as both fibrosarcoma and chondrosarcoma metastasize at a later stage of the disease than does true osteogenic sarcoma. Only 8.5 per cent of the 59 patients with five-year survivals died of their disease. The authors claim that if a patient with osteogenic sarcoma lives five years his chances of escaping further advance of the process are 12 to 1.

The malignant potentialities of abnormally situated cartilage (enchondroma or osteochondroma) have been stressed.[75] Where feasible, the complete surgical extirpation of such lesions is recommended. The histologic diagnosis of benign chondroma and chondromyxoma does not preclude possible local recurrence or distant metastases. Any alteration in the appearance of such lesions should arouse suspicion of malignant transformation.

The development of sarcomatous degeneration in Paget's disease is not uncommon and is a serious portent. Seven of Platt's[76] 10 patients so afflicted died within one year. The occurrence of sarcoma in pre-existent areas of fibrous dysplasia or fibrocystic disease is a rare manifestation only recently recognized — and also heralds a dismal prognosis. Three of four cases reported terminated fatally.[76, 77] Although many cases of fibrous dysplasia or fibrocystic disease have been seen in the Massachusetts General Hospital for relatively short periods of time (five to ten years), no malignant degeneration has been observed.

Reticulum-cell sarcoma. An over-all presentation of this type of tumor is to be found in a recent article by Coley, Higinbotham and Groesbeck.[78] After a review of the history and incidence of the entity, its characteristic clinical and pathologic features, based on a study of 37 proved cases, are described, and the value of x-ray therapy is pointed out.

The diagnostic roentgenologic changes of reticulum-cell sarcoma of bone have been well described by Sherman and Snyder,[79] whose conclusions have been based on roentgenograms of 17 proved cases. In brief, they found that the tumor occurs most often in long bones without significant localization in a given bone and without constant symmetry or configuration. Destruction of bone is invariable and usually outweighs productive changes. In structure the tumor shows a patchy arrangement of areas of destruction, often associated with similar-sized areas of production without definite boundary. The bone cortex is destroyed without evidence of expansion or thickening. There may or may not be evidence of periosteal and adjacent joint change with accompanying synovitis. Pathologic fracture occurs in about 25 per cent of these tumors. A primary reticulum-cell sarcoma of bone is usually solitary; if untreated it grows rapidly but retains its initial characteristics; its response to radiation therapy is usually good.

The acceptance of reticulum-cell sarcoma of bone as an entity is relatively new. Because it has not been well known as an isolated lesion, it seems possible that many so-called cured cases of Ewing's tumor reported in the past may actually have been reticulum-cell sarcomas. In view of this a review of histologic sections of these lesions would be of interest.

The importance of x-ray examination of the skeleton in children in whom leukemia is suspected is emphasized by Kalayjian, Herbut and Erf.[81] This is particularly true when the clinical findings are indefinite. Bone changes associated with leukemia may be nonspecific, but the diagnosis should be seriously entertained in cases showing evidence of bone destruction, expansion of the marrow cavity, demineralization, periosteal elevation and decalcification of the metaphyses.

That involvement of bone in lymphoma or allied disease may be confused with hyperparathyroidism is worth noting. Van der Sar and Hartz[81] report a case in which there was marked decalcification of the skeleton and in which the clinical findings indicated hyperparathyroidism. The patient died of uremia; the anatomic diagnosis was lymphosarcoma.

Myeloma. Some cases of myeloma may also simulate hyperparathyroidism. The question of the existence of a solitary myeloma as an entity is raised by Christopherson and Miller.[82] They discuss a group of cases that were observed for three years without evidence of dissemination, and they conclude, on the basis of roentgenographic studies of the remainder of the skeleton and bone-marrow and hematologic findings, that plasma cells are present in the solitary tumor whereas myeloma cells characterize the multiple myelomas. This point has theoretical interest, but to judge by our experience most patients with solitary myeloma, if they live a significant length of time, develop multiple foci. This emphasizes the fact that myeloma progresses at a leisurely pace, an observation confirmed by Bayrd and Heck.[83]

For those desiring a thorough review of the subject of multiple myeloma the investigations of Lichtenstein and Jaffe[84] are recommended.

That myeloma occurs not only in adult life but also in childhood is pointed out by Jansson,[85] who reviews the literature and reports an additional case. He states that in a group of 9 children the major changes were found about the hip and other large joints, — the ribs and skull seemingly being spared. Spinal changes, — marked expansion of the intervertebral disk spaces, — are manifest.

Recent suggestions that x-ray therapy might be of consistent value in myeloma have been disproved by Garland and Kennedy.[86] These lesions, except in an occasional case, proved to be radioresistant. These authors' recommendation that solitary myelomas be adequately irradiated seems inconsistent, as at the same time they question the existence of this entity.

The roentgenologic features of *neurofibromatosis* have been discussed by Holt and Wright.[87] General surveys were made on 97 patients; in 37, some skeletal defects more or less corresponding to the clinical manifestations of the disease were demonstrated. In some cases also notching of the ribs, long considered a pathognomonic sign of coarctation of the aorta but in this instance resulting from neurofibromatous pressure and erosion, was noted. Unilateral notching of the ribs associated with the tetralogy of Fallot has been reported by Batchelder and Williams.[88]

(To be concluded)

References

1. Sosman, M. C. Specificity and reliability of roentgenographic diagnosis. *New Eng. J. Med.* **242**:849-855, 1950.
2. Mallory, T. B. Pathology: diseases of bone. *New Eng. J. Med.* **227**: 955-960, 1942.
3. Schinz, H. R., Baensch, W. E., Friedl, E., and Uehlinger, E. *Lehrbuch der Roentgendiagnostik.* Stuttgart: Georg Thieme, 1950.
4. Coley, B. L. *Neoplasms of Bone and Related Conditions.* 765 pp. New York: Paul B. Hoeber, 1949.
5. Albright, F., and Reifenstein, E. C., Jr. *The Parathyroid Glands and Metabolic Bone Disease.* 393 pp. Baltimore: Williams & Wilkins Co., 1948.
6. Weinmann, J. P., and Sicher, H. *Bone and Bones: Fundamentals of bone biology.* 464 pp. St. Louis: C. V. Mosby Co., 1947.
7. Caffey, J. Pediatric x-ray diagnosis. *Radiology* **51**:111-113, 1948.
8. Todd, T. W., et al. *Atlas of Skeletal Maturation.* 203 pp. St. Louis: C. V. Mosby Co., 1937.
9. Elgenmark, O. Normal development of ossific centres during infancy and childhood: clinical, roentgenologic, and statistical study. *Acta paediat.* (Supp. 1) **33**:1-79, 1946.
10. Kelly, H. J., and Reynolds, L. Appearance and growth of ossification centers and increases in body dimensions of white and Negro infants. *Am. J. Roentgenol.* **57**:477-516, 1947.
11. Christie, A. Prevalence and distribution of ossification centers in newborn infants. *Am. J. Dis. Child.* **77**:355-361, 1949.
12. Maresh, M. M. Growth of major long bones in healthy children: preliminary report on successive roentgenograms of extremities from early infancy to twelve years of age. *Am. J. Dis. Child.* **66**: 227-257, 1943.
13. Anderson, M., and Green, W. T. Lengths of femur and tibia: norms derived from orthoroentgenograms of children from five years of age until epiphyseal closure. *Am. J. Dis. Child.* **75**:279-290, 1948.
14. Poulhès, J. Les noyaux d'ossification du membre inférieur chez l'enfant jusqu'à 2 ans. *J. de radiol. et d'électrol.* **30**:124-126, 1949.
15. Lurie, L. A., Levy, S., and Lurie, M. L. Determination of bone age in children: method based on study of 1129 white children. *J. Pediat.* **23**:131-140, 1943.
16. Pyle, S. I., et al. Substitute for skeletal age (Todd) for clinical use: red graph method. *J. Pediat.* **32**:125-136, 1948.
17. Reynolds, E. L., and Sontag, L. W. Seasonal variations in weight, height, and appearance of ossification centers. *J. Pediat.* **24**: 524-535, 1944.
18. Woolley, P. V., Jr., and McCammon, R. W. Bone growth in congenital myxedema: use of serial roentgenograms of os radius in diagnosis and regulation of therapy during infancy. *J. Pediat.* **27**:229-235, 1945.
19. Henderson, S. G., and Sherman, L. S. Roentgen anatomy of skull in newborn infant. *Radiology* **46**:107-118, 1946.
20. Rathbun, J. C. "Hypophosphatasia," new developmental anomaly. *Am. J. Dis. Child.* **75**:822-831, 1948.
21. Caffey, J. Prenatal bowing and thickening of tubular bones, with multiple cutaneous dimples in arms and legs: congenital syndrome of mechanical origin. *Am. J. Dis. Child.* **74**:543-562, 1947.
22. Heyman, C. H., and Herndon, C. H. Congenital posterior angulation of tibia. *J. Bone & Joint Surg.* **31-A**:571-580, 1949.
23. Barber, C. G. Osteochondrosis deformans tibiae: nonrachitic bow leg in children. *Am. J. Dis. Child.* **64**:831-842, 1942.
24. Neuhauser, E. B. D., Wittenborg, M. H., and Dehlinger, K. Diastematomyelia: transfixation of cord or cauda equina with congenital anomalies of spine. *Radiology* **54**:659-664, 1950.
25. Borovsky, M. P., and Arendt, J. Chondrodystrophia calcificans congenita. *J. Pediat.* **24**:558-567, 1944.
26. Fairbank, H. A. T. Dysplasia epiphysialis punctata. *J. Bone & Joint Surg.* **31-B**:114-122, 1949.
27. Neuhauser, E. B. D. Personal communication.

28. Neuhauser, E. B. D., Shwachman, H., Wittenborg, M. H., and Cohen, J. Progressive diaphyseal dysplasia. *Radiology* **51**:11-22, 1948.
29. Sear, H. R. Engelmann's disease: osteopathia hyperostotica sclerotisans multiplex infantilis: report of case. *Brit. J. Radiol.* **21**:236-241, 1948.
30. Ribbing, S. Hereditary, multiple, diaphyseal sclerosis. *Acta radiol.* **31**:522-536, 1949.
31. Caffey, J., and Silverman, W. A. Infantile cortical hyperostoses: preliminary report on new syndrome. *Am. J. Roentgenol.* **54**: 1-16, 1945.
32. Caffey, J. Infantile cortical hyperostoses. *J. Pediat.* **29**:541-559, 1946.
33. Smyth, F. S., Potter, A., and Silverman, W. Periosteal reaction, fever and irritability in young infants: new syndrome? *Am. J. Dis. Child.* **71**:333-350, 1946.
34. Sherman, M. S., and Hellyer, D. T. Infantile cortical hyperostosis: review of literature and report of five cases. *Am. J. Roentgenol.* **63**:212-222, 1950.
35. Caffey, J. Multiple fractures in long bones of infants suffering from chronic subdural hematoma. *Am. J. Roentgenol.* **56**:163-173, 1946.
36. Glaser, K. Double contour, cupping and spurring in roentgenograms of long bones in infants. *Am. J. Roentgenol.* **61**:482-492, 1949.
37. Tucker, F. R. Arterial supply to femoral head and its clinical importance. *J. Bone & Joint Surg.* **31-B**:82-93, 1949.
38. Albright, F., Burnett, C. H., Smith, P. H., and Parson, W. Pseudohypoparathyroidism — example of "Seabright-bantam Syndrome": report of three cases. *Endocrinology* **30**:922-932, 1942.
39. Brailsford, J. F. Familial brachydactyly. *Brit. J. Radiol.* **18**:167-172, 1945.
40. Baylin, G. J., and Glenn, J. C., Jr. Soft tissue changes in early acute osteomyelitis. *Am. J. Roentgenol.* **58**:142-147, 1947.
41. McAdam, I. W. J. Penicillin treatment of acute haematogenous osteomyelitis. *Brit. J. Surg.* **33**:167-172, 1945.
42. Altemeier, W. A., and Reinecke, H. G. Roentgenographic interpretation of acute hematogenous osteomyelitis treated with penicillin. *Am. J. Roentgenol.* **54**:437-448, 1945.
43. Higley, G. B., and Rude, J. C. Roentgenographic changes in bone infections treated with penicillin. *Radiology* **44**:115-124, 1945.
44. Hutter, C. G., Jr. New concepts of osteomyelitis in newborn infant. *J. Pediat.* **32**:522-529, 1948.
45. Texter, E. C., Irwin, W. A., and Kaump, D. H. Roentgenologic findings in osteomyelitis following bone marrow infusions in infants: review of literature and report of two cases. *Am. J. Roentgenol.* **62**:534-540, 1949.
46. Feuchtwanger, J. L. Multiple tuberculous lesions of spine. *Brit. J. Radiol.* **21**:400-405, 1948.
47. Leader, S. A. Tuberculosis of ribs. *Am. J. Roentgenol.* **63**:354-359, 1950.
48. Isaacson, A. S., and Whitehouse, W. M. Spontaneous sacro-iliac obliteration in patients with tuberculosis. *J. Bone & Joint Surg.* **31-A**: 306-311, 1949.
49. Sasbin, D., Brown, G. N., Laffer, N. C., and McDowell, H. C. Disseminated coccidioidomycosis localized in bones. *Am. J. M. Sc.* **212**:565-573, 1946.
50. Rhinehart, W. J., and Bauer, J. T. Disseminated granuloma inguinale of bones. *Am. J. Roentgenol.* **57**:562-567, 1947.
51. Bellini, M. A. Osteohydatidosis: its radiological features. *Radiology* **47**:569-574, 1946.
52. Collins, V. P. Bone involvement in cryptococcosis (torulosis). *Am. J. Roentgenol.* **63**:102-112, 1950.
53. Metcalfe, J. W. Importance of leprosy in orthopedic surgery. *U. S. Nav. M. Bull.* **48**:656-667, 1948.
54. Hodgson, J. R., Pugh, D. G., and Young, H. H. Roentgenologic aspect of certain lesions of bone: neurotrophic or infectious? *Radiology* **50**:65-70, 1948.
55. Cooper, G., Jr., Adair, N., and Patterson, W. M. Familial osseous atrophy. *Radiology* **48**:509-513, 1947.
56. Bromer, R. S. Giant cell tumor of bone. *Proc. New Eng. Roentgen Ray Soc.* **6**:80-95, 1950.
57. Andersen, S. R. Malignancy of giant cell tumors: study on giant cell tumors and allied affections in bone, with reference specially to their malignancy. *Acta radiol.* **26**:11-35, 1945.
58. Lichtenstein, L. Giant-cell tumor of bone. *J. Bone & Joint Surg.* **33-A**: 143-150, 1951.
59. Brailsford, J. F. Diagnosis and treatment of osteoclastoma. *Radiology* **43**:35-38, 1944.
60. Jaffe, H. L. Tumors of skeletal system: pathological aspects. *Bull. New York Acad. Med.* **23**:497-511, 1947.
61. Buschke, F., and Cantril, S. T. Roentgentherapy of benign giant-cell tumor of bone. *Cancer* **2**:293-315, 1949.
62. Lichtenstein, L., and Kaplan, L. Benign chondroblastoma of bone: unusual localization in femoral capital epiphysis. *Cancer* **2**:793-798, 1949.
63. Coley, B. L., and Santora, A. J. Benign central cartilaginous tumors of bone. *Surgery* **22**:411-423, 1947.
64. Lichtenstein, L. Aneurysmal bone cyst: pathological entity commonly mistaken for giant-cell tumor and occasionally for hemangioma and osteogenic sarcoma. *Cancer* **3**:279-289, 1950.
65. Heublein, G. W., and Baird, C. L. Solitary unicameral bone cyst of right ilium: case report. *Am. J. Roentgenol.* **59**:699-704, 1948.
66. Jaffe, H. L., and Lichtenstein, L. Chondromyxoid fibroma of bone: distinctive benign tumor likely to be mistaken especially for chondrosarcoma. *Arch. Path.* **45**:541-551, 1948.
67. Longstreth, H. P., Blanco, P., and Sanes, S. Myxochondrosarcoma of talus. *J. Bone & Joint Surg.* **30-A**:774-778, 1948.
68. Jaffe, H. L. Osteoid-osteoma of bone. *Radiology* **45**:319-334, 1945.
69. Moberg, E. Natural course of osteoid osteoma. *J. Bone & Joint Surg.* **33-A**: 166-170, 1951.
70. Lichtenstein, L., and Jaffe, H. L. Ewing's sarcoma of bone. *Am. J. Path.* **23**:43-77, 1947.
71. McSwain, B., Byrd, B. F., Jr., and Inman, W. O., Jr. Ewing's tumor. *Surg., Gynec. & Obst.* **89**:209-221, 1949.
72. Holmes, G. W., and Schulz, M. D. *Therapeutic Radiology.* 347 pp. Philadelphia: Lea & Febiger, 1950.
73. Prevo, S. B. Clinical analysis of 205 cases of malignant bone tumors. *J. Bone & Joint Surg.* **32-A**:298-306, 1950.
74. Coley, B. L., and Harrold, C. C., Jr. Analysis of 59 cases of osteogenic sarcoma with survival for five years or more. *J. Bone & Joint Surg.* **32-A**:307-310, 1950.
75. Coley, B. L., and Higinbotham, N. L. Significance of cartilage in abnormal locations. *Cancer* **2**:777-788, 1949.
76. Platt, H. Sarcoma in abnormal bones. *Brit. J. Surg.* **34**:232-239, 1947.
77. Coley, B. L., and Stewart, F. W. Bone sarcoma in polyostotic fibrous dysplasia. *Ann. Surg.* **121**:872-881, 1945.
78. Coley, B. L., Higinbotham, N. L., and Groesbeck, H. P. Primary reticulum-cell sarcoma of bone: summary of 37 cases. *Radiology* **55**:641-658, 1950.
79. Sherman, R. S., and Snyder, R. E. Roentgen appearance of primary reticulum cell sarcoma of bone. *Am. J. Roentgenol.* **58**:291-306, 1947.
80. Kalayjian, B. S., Herbut, P. A., and Erf, L. A. Bone changes o leukemia in children. *Radiology* **47**:223-233, 1946.
81. Van der Sar, A., and Hartz, P. H. Skeletal lymphosarcomatosis with secondary hyperparathyroidism. *Am. J. Clin. Path.* **16**:701-713, 1946.
82. Christopherson, W. M., and Miller, A. J. Re-evaluation of solitary plasma-cell myeloma of bone. *Cancer* **3**:240-252, 1950.
83. Bayrd, E. D., and Heck, F. J. Multiple myeloma: review of eighty-three proved cases. *J. A. M. A.* **133**:147-157, 1947.
84. Lichtenstein, L., and Jaffe, H. L. Multiple myeloma: survey based on 35 cases, 18 of which came to autopsy. *Arch. Path.* **44**:207-246, 1947.
85. Jansson, G. Roentgenologic skeletal changes in myeloma in childhood (platyspondylia generalisata myelomatosa). *Acta radiol.* **27**:73-80, 1946.
86. Garland, L. H., and Kennedy, B. R. Roentgen treatment of multiple myeloma. *Radiology* **50**:297-317, 1948.
87. Holt, J. F., and Wright, E. M. Radiologic features of neurofibromatosis. *Radiology* **51**:647-663, 1948.
88. Batchelder, P., and Williams, R. J. Notching of ribs without coarctation. *Radiology* **51**:826-830, 1948.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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BENJAMIN CASTLEMAN, M.D., *Associate Editor*

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CASE 37271

PRESENTATION OF CASE

A forty-two-year-old man was admitted to the hospital because of a tumor of the jaw.

More than a year before admission the patient noted an asymptomatic lump in the right mental area of the mandible. This was removed by curettage by an oral surgeon four months before entry and was reported as benign. The lesion recurred, and at the time of entry the mass was about the same size as it was originally.

Physical examination showed a healthy-appearing man. There was a bone-hard, insensitive, smooth-surfaced, fixed mass measuring about 3 x 4 cm., involving the lateral and inferior aspect of the right mandible. There was no abnormality of the mucous membrane. The only other physical abnormalities were slight anisocoria and three tiny hemangiomatous spots over the abdomen.

The blood pressure was 130 systolic, 90 diastolic.

A urinalysis was normal. Examination of the blood showed a hemoglobin of 15.3 gm. An x-ray film of the mandible demonstrated a soft-tissue mass involving the anteroinferior portion of the mandible, extending chiefly to the right. Irregular destructive changes were observed in the horizontal ramus of the right mandible, extending to the midline and also involving the anterior portion of the left horizontal ramus. Within the soft-tissue tumor were visible calcified streaks lying perpendicular to the bone. The calcification appeared to arise from the mandibular periosteum (Fig. 1). X-ray films taken elsewhere five months before entry (one month before the curettage) were essentially similar.

On the second hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. ERNEST M. DALAND*: I inquired about the removal of the lump in the right mental area and was told that it was done through the mouth. It is interesting that even though the incision had been made through the mucous membrane into the jaw, four months later there was no ulceration of the mucous membrane.

May I see the x-ray films?

DR. STANLEY M. WYMAN: The films were taken over a five-month period. During this entire period of time the lesion can be seen as essentially unchanged. It consists of an area of bone destruction, rather irregular and somewhat broken in contour, surrounded by some bone sclerosis (Fig. 1). The lesion appears to extend into the center of the mandible anteriorly, as seen in the anteroposterior view.

FIGURE 1. *X-ray Film of Jaw. Arrows point to margin of lesion.*

Two small contact films show definite periosteal new-bone formation with bony spicules perpendicular to the main contour of the mandible.

DR. DALAND: The two contact films seem to be the important diagnostic films. The others show the general location of the mass and that it had been present for several months without much change in size. You will note that this man is edentulous at forty-two years. There was not much in the history that will help me except the local examination.

What are some of the possibilities for a lesion in this part of the body? One thing I must not lose sight of is the possibility that he had a metastatic lesion in the jaw from some other focus. There was nothing in the history or physical examination that suggested that he had ever had any other neoplastic lesion. I recall seeing two patients with tumors of the jaw, one of which was ulcerated and the other was not. One patient had a known carcinoma of the jaw and the other one did not. We were much

*Visiting surgeon, Massachusetts General Hospital.

chagrined to have the pathologist look at the section and tell us that if we examined the rectum we would find the primary lesion — and he was right. The x-ray findings do not suggest a metastatic lesion, but it is something to be kept in mind. Most carcinomas of the jaw, so called, are primary carcinomas of the mucous membrane with invasion of the jaw. Epidermoid carcinomas are rarely found in the jaw unless a primary focus is found. However, I have had one patient with epidermoid carcinoma of the jaw who had a complete resection of the jaw — and no point of entry was found; nothing else ever showed up, so it seemed likely that it arose from a tooth socket, although there was no such history. With carcinoma of the jaw one expects to find an ulcerated lesion in the mouth along with the destructive areas in the jaw.

I know nothing at all about the Hinton test on this patient, but I think the lesion was not syphilitic.

Adamantinoma is another possibility. The x-ray findings are not in line with a diagnosis of adamantinoma. Ordinarily a hard nonulcerated lesion is found, but on x-ray examination cystic areas are seen within the larger tumor. There is nothing here to suggest cyst formation, but many times an adamantinoma cannot be diagnosed except by biopsy.

It seems to me that the most probable diagnosis here is osteogenic sarcoma. I have a report that the tissue from the first curettage was reported as benign. The pathologist reports on the tissue he is given. It is quite likely that the first surgeon did not reach the involved area. He may have removed some sclerotic bone secondary to the malignant process. Certainly in the films the most characteristic part of the tumor is along the lower border, which could not be reached through the mouth except by complete resection of the mandible. Osteogenic sarcoma of the jaw is a less malignant type of sarcoma than that found in the long bones. It does not have the same tendency to metastasize — certainly not as early as osteogenic sarcomas of the long bones. It may run quite a long course before it breaks through or before the attention of the physician is called to it, but it is nevertheless a lethal lesion if it is not completely removed. It is not surprising to see very little change in this condition over a four-month period.

This lesion in a forty-two-year-old man had destructive and sclerosing areas, but most important was the involvement of the periosteum — a break in the periosteum and a sun-ray formation of tiny areas of calcification at right angles to the mandible. That usually means osteogenic sarcoma, but not always. If he had a fracture through the mandible, I would expect to find irregularity during the process of repair and even calcification out in the soft parts, not rays of this sort. I believe, therefore, that this man had an osteogenic sarcoma of the mandible.

Dr. Grantley Taylor: It is very interesting that the sections of the tissue removed four months before admission apparently were not only reviewed by the local pathologist but were sent to several others. The report was fibrous dysplasia with invasion. I finally tracked down these slides before I operated on the patient and gave them to Dr. Castleman, who said that it was not fibrous dysplasia but low-grade sarcoma. The clinical behavior certainly was not consistent with fibrous dysplasia, about which I am sorry to say I cannot give you any learned discourse. It is a very mystifying process to me in any case. Certainly in this case the physical and x-ray appearance did not even suggest it.

The radiologist was of the opinion that we were dealing with a malignant tumor, on the grounds that the area of destruction was irregular, diffuse and not circumscribed in any way and had none of the characteristics of a benign process. At any rate, the patient was a healthy man with a tumor of the jaw, which it was a simple matter to resect. He made an excellent convalescence and went home on the seventh day. We did a tracheotomy as a safety measure because we resected the midline, and under those circumstances patients may have postoperative complications due to lack of control of the tongue and airway. We took the tube out on the second day and the wound was closed. It had healed by the time of discharge from the hospital.

Clinical Diagnosis

Osteogenic sarcoma of mandible.

Dr. Daland's Diagnosis

Osteogenic sarcoma of mandible.

Anatomical Diagnosis

Osteogenic sarcoma of mandible.

Pathological Discussion

Dr. Tracy B. Mallory: For a number of years before Lichtenstein and Jaffe* described the condition that he termed fibrous dysplasia, it had been recognized that around the jaws, more commonly in the maxilla than in the mandible, benign bone-forming tumors were rather frequent. They have been described under several different names. One that we used in this hospital for many years was ossifying fibroma. Particularly in jaw lesions this process may closely mimic osteogenic sarcoma, and the differential diagnosis is not easy to make. Most pathologists have learned to be cautious of making the diagnosis of osteogenic sarcoma in a jaw mass unless the findings are extremely typical. I think Dr. Castleman is to be congratulated for recognizing this as a sarcoma. I am not perfectly sure that I would have done so myself on the original sections submitted to us, although the subsequent course of

*Lichtenstein, L., and Jaffe, H. L. Fibrous dysplasia of bone. *Arch. Path.* 33:777-816, 1942.

the lesion and the sections from the recent resection left no doubt about the matter.

CASE 37272

Presentation of Case

A forty-four-year-old woman was admitted to the hospital because of "biliousness and anemia."

Fourteen years before admission the patient had a cholecystectomy because of "colic"; at this time she was told that she had a "harmless little tumor of the stomach." According to a report from the hospital, this was removed and pathological examination revealed a fibroma. Since operation she had had rare bouts of nausea and vomiting after heavy meals, but these had gradually diminished. Occasionally, however, she noted a "knotted" feeling in the midepigastrium, gaseousness and right subcostal pain radiating around to the scapula. About three months before entry friends noted that she was becoming pale, and she noted tarry stools, which continued to the time of admission. The hemoglobin was found to be 40 per cent and the stools guaiac positive; a gastrointestinal series and barium-enema examination were negative. She had frequent headaches during these three months. Her appetite had remained fairly good. There was no statement concerning weight loss. One week before admission she was admitted to another hospital, where three blood transfusions were given; she was then transferred to this hospital.

Physical examination revealed a well developed, pale, middle-aged woman. There were no palpable lymph nodes. The heart and lungs were normal. Examination of the abdomen showed a diagonal right-upper-quadrant scar and a small umbilical fascial defect; there was no tenderness and no palpable organs or masses.

The blood pressure was 130 systolic, 80 diastolic.

The hemoglobin was 13.4 gm. and the white-cell count 5200. A blood Hinton test was negative. The van den Bergh test was 0.2 mg. direct and 0.3 mg. total and the total protein 6.5 gm. per 100 cc. The prothrombin time was 18 seconds. One stool was guaiac negative. An x-ray film of the chest and barium-enema examination were normal. A gastrointestinal series showed a normal esophagus; in the stomach there was an irregular filling defect along the lesser curvature side of the posterior wall, extending from the fundus downward, involving approximately half the body (Fig. 1). Within this defect there was a large ulceration measuring 2 cm. in diameter and about 2 cm. deep; it appeared to be intraluminal in position. The remainder of the stomach and visualized duodenum and jejunum were within normal limits.

On the fifth hospital day an operation was performed.

Differential Diagnosis

Dr. Stanley M. Wyman*: Being a radiologist, I shall begin by showing the films. The examination of the chest was within normal limits. The barium-enema examination was noncontributory. In the films from the upper-gastrointestinal series taken in this hospital the area in question is outlined very well, and I shall leave these films for your study while I discuss the case.

The history seems to me noncontributory and at the same time perhaps very enticing. Cholecystectomy fourteen years before entry leaves me with very little ground for discussion. However, at that time the patient was said to have a harmless little tumor of the stomach, which was described pathologically as a fibroma. I do not know whether this was really a fibroma or a leiomyoma, the latter being much more common, I believe. The history from that point on was rather indefinite, consisting of a vague "knotted" feeling in the epigastrium, some nausea and vomiting after heavy meals, gaseousness and right subcostal pain. All of those, so far as I am concerned, are not much help in the diagnosis. However, three months before entry she was noted by her friends to have become pale — and that, of course, is a very real finding. At that

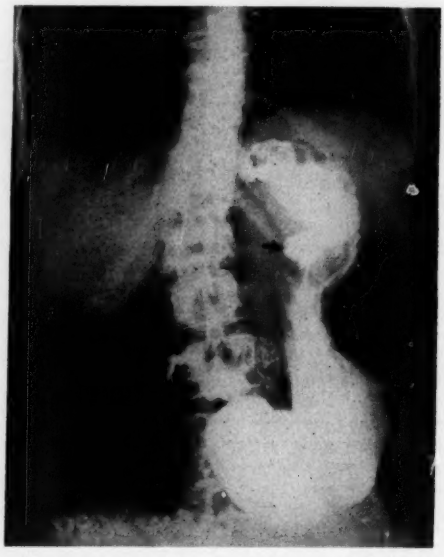

Figure 1. *X-ray Film from Gastrointestinal Series. Arrow points to rectangular pooling of barium.*

*Radiologist, Massachusetts General Hospital.

time she had tarry stools, so I know she was having considerable bleeding from the gastrointestinal tract. Since the blood was tarry, it is most likely that the bleeding came from high up in the gastrointestinal tract. The statement is made that a gastrointestinal series in another hospital was negative. However, the films that were obtained approximately one month before her admission to this hospital showed, on review, the same lesion that was found here. I think I must take the statement that the upper-gastrointestinal series was negative to mean that no lesion was found, but I am hard put to it to believe that no lesion was present.

To continue the history, her appetite remained good, but there is no statement about weight loss. The physical examination was remarkably negative except for the pallor. The hemoglobin of 13.4 gm. was obtained after she had had three blood transfusions elsewhere. One stool examination here was guaiac negative. I am sorry more were not done. I think they might have been positive.

This patient had a picture that consisted primarily of a vague upper-gastrointestinal complaint and definite gastrointestinal-tract bleeding, and by x-ray examination she had a lesion in the stomach that appeared without much question to be a surgical problem. The exact nature of the lesion is open to speculation. Up to the present I have not made up my mind exactly what it is.

There are a number of pieces of additional information that might have been of tremendous help. I should like to know, if possible, the gastric acidity. This might be of some help in ruling carcinoma in or out. It is quite possible, of course, to have carcinoma and free hydrochloric acid, but nonetheless it is a straw in the wind. Today cytologic examinations are being done so commonly that it might have been of interest to perform this type of examination on this patient, although the degree of accuracy on gastric washings is not as high as in other parts of the body. Lastly, of course, gastroscopy, if it could have been accomplished without danger, would have been of considerable interest and might have made the definitive diagnosis. However, you will notice that the lesion began in the stomach very close to the esophageal orifice and extended downward in a somewhat polypoid fashion, so the gastroscope might have run into difficulty if it had been passed.

Turning to the x-ray films themselves, I am confronted with a massive lesion involving the proximal third of the stomach. The lesion is roughly rounded and as nearly as one can tell is protruding into the stomach to a rather pronounced degree. This is very well seen on the plain films, in which there is some gas outlining the lesion. On one of these films there seems to be a rounded upper border to the mass in question. In the second film, which was taken somewhat later and perhaps in a different projection, there is less suggestion of a rounded upper border. The ulceration described in the protocol is this large, rather rectangular pooling of barium, which certainly seems to lie within the mass described (Fig. 1). I think it is open to question whether or not the ulceration may extend further up into the superior portion of the mass just above the frank ulcer crater. This is a point I cannot prove or disprove from the films at hand.

What are some of the possibilities? Among the benign conditions that I think of is localized giant gastritis, which may present a real mass as confusing as this one. I have not seen one as large as this, however, or the central ulceration that is seen in this case. Benign gastric ulcer associated with gastritis is quite unlikely, since this ulcer appears to be within the lesion rather than protruding beyond the wall of the stomach. Syphilis — gumma of the stomach — I think can be dismissed as extremely rare and extremely unlikely, particularly with a negative serologic test. Aside from the inflammatory processes, one might consider in passing extremely large gastric varices, but the patient does not have enlargement of the spleen, the greater curvature of the stomach is not involved and the esophagus was grossly normal. I think I can discard that possibility.

The tumors are many. The most common type of tumor, of course, is a polypoid fungating carcinoma of the stomach, which I think must be given serious consideration. It is commonly as silent as this symptomatically, but I think there has been an unusual degree of bleeding in this case for carcinoma of the stomach. Lymphoma is in much the same category, and I cannot draw a real differential diagnosis between lymphoma and carcinoma. An extreme degree of polyposis might be mentioned, but only in passing. It is extremely unlikely that it would have reached this degree while confined to only one small portion of the stomach.

Interesting possibilities such as angioma must be borne in mind, especially with the large central ulceration and the pronounced degree of bleeding. I should like to know whether the lesion looked flexible fluoroscopically. This is the sort of mass concerning which one would be much helped by seeing the stomach fluoroscopically and by being able to palpate the lesion.

The story of fibroma in the past makes me wonder about its being a fibroma, a leiomyoma or a leiomyosarcoma. I believe the leiomyomas and the leiomyosarcomas are more common than fibromas. I am unable to give any good reason that this was not a leiomyoma or a leiomyosarcoma; they are commonly rather silent lesions as far as symptoms are concerned. They often produce considerable bleeding in the gastrointestinal tract. The large ulcer crater of which I can be certain was a rather typical punched-out one such as occurs with leiomyomas or leiomyosarcomas, but this type of lesion is less common than the polypoid type of carcinoma. Ulcera-

tion of this degree is more common in leiomyomas. I think I shall put my first money on a polypoid carcinoma and leave leiomyoma as my second choice.

DR. JACOB LERMAN: Not long ago I had a patient who had a lesion in the upper part of the stomach not unlike this one; it consisted of a penetrating benign ulcer with walled-off inflammatory reaction so that the patient presented a tumor mass. Eventually it penetrated into the spleen and into the pancreas, which had to be removed in toto.

DR. WYMAN: That is a definite possibility, Dr. Lerman. I discarded it primarily because of the appearance of the mass within the stomach. That could have been an inflammatory mass that had formed and pressed secondarily on the stomach.

CLINICAL DIAGNOSIS

?Carcinoma of stomach.

DR. WYMAN'S DIAGNOSIS

?Polypoid carcinoma, ?leiomyoma of stomach.

ANATOMICAL DIAGNOSIS

Leiomyosarcoma of stomach.

PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: This patient was operated on by Dr. Marshall K. Bartlett, who found a large, apparently well circumscribed, almost spherical tumor in the gastric wall, located on the greater curvature. Sections of it showed a spindle-cell tumor of a type that has most often been called a leiomyosarcoma. However, these tumors often look so different from the leiomyosarcomas of the uterus that some doubt has been raised whether that is really a correct histologic diagnosis. In a few cases very well differentiated features characteristic of neurofibroma or schwannoma have been seen, suggesting that at least portions of these tumors arise from the nerve plexuses of the stomach walls rather than from muscular layers. In the more malignant undifferentiated lesions I think a distinction is often impossible, and it probably makes no difference in prognosis or in treatment. In this case I thought a smooth-muscle origin was the most probable one — and we called this leiomyosarcoma. It was growing with considerable rapidity, and the prognosis must be guarded. Some of these cases develop metastases to the liver.

In some of these tumors a very peculiar type of ulceration develops — a long, slender ulcer that extends deep into the center of the tumor with almost the appearance of a fistulous tract; then, when the center of the tumor is reached, it branches out rather like an inverted mushroom in shape. Occasionally the radiologist is fortunate enough to be able to fill the entire tract with barium so that it shows up clearly in the plates; in that case he can make a diagnosis of spindle-cell tumor of the stomach with considerable confidence. There is no way in which the radiologist could distinguish a leiomyoma from a schwannoma, since the gross appearance of these two tumors is identical, and there is also no way, so far as I know, by which he could decide whether the tumor was to be regarded as benign or malignant. That, too, is not altogether easy to decide histologically. A tumor that one would not regard with any particular fear in the uterus must be considered probably malignant when its origin is the intestinal tract. These tumors are often multiple in the stomach. Pathologists who have been particularly interested in the subject have examined stomachs at post-mortem examinations with great care by running every square centimeter of the gastric wall between their fingers in order to feel the slightest little shot-like focus. It is not rare to find 5 or 10 minute tumors in a single stomach, which, of course, are so small that they would never produce symptoms and could not be visualized by x-ray examination. But any one of them might in the course of time grow to a large size and produce a picture such as this. My guess would be that this case does not represent a recurrence of a tumor removed during the previous operation but a new and probably similar tumor arising at a separate spot in the stomach wall.

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POINT 4 PROGRAM—HEALTH CREDO

"We believe that health improvement in all parts of the world is one of the main roads to peace." This belief, already one of the cornerstones of the United States Point 4 program, was reaffirmed early in May by Dr. Leonard Scheele as he accepted the office of president of the World Health Organization and outlined WHO's role in improving conditions throughout the world.[1] Health is a universal aspiration, but as a "road to peace" it may prove to be uncomfortably bumpy and surprisingly circuitous.

What well-intentioned political and medical leaders appear to ignore is that the health of persons and the health of nations, although related, are facts of as different orders as are microcosms and macrocosms. The experience of Germany has shown that individuals can be enjoying good physical health while the nation to which they belong is taking the road to war. Surely aggressive warfare may be considered a manifestation of national ill health. The histories of Italy and Puerto Rico have shown that to control disease by modern measures that promote the health of individuals is to be confronted in a limited land area with insupportable increases of population that seek room in which to live by almost any means, peaceful or violent. China and Korea have shown that under appropriate circumstances healthy members of human herds channel into predatory migration almost as easily as grasshoppers. The experiment of feeding India's teeming millions is being made, but from an ecologic standpoint this is no simple matter of philanthropy. The ecologic question is: How valid is the naïve belief that health improvement in all parts of the world is one of the main roads to peace? The belief is comforting, humanitarian and Christian. Is it well founded?

Anyone who has ever worked in a garden, mowed a lawn, kept an aquarium or dogs, seeded a test tube with micro-organisms, hunted or fished or even passed an eighth-grade course in biology may be pardoned if he doubts the truth of our surgeon general's statement. It is a half-truth, just as America's health administration of Puerto Rico has been a half-success. To institute all available health measures for a people, to supply them with all needed food and to make no provision for a balance between births and deaths within a limited land area may be to sow dragons' teeth — not for Dr. Scheele but for his children and his children's children to reap. Cadmus undoubtedly had the best of intentions when he sowed his strange seed, but he harvested a crop of armed warriors — and the legend makes no mention of their being in ill-health, for they fell on each other and fought until only five were left. At this point, we are told, the most sensible one of the five said: "Brothers, let us live together in peace."

The modern ecologist is wondering [2-4] where the magnificent Mother-Ceres-like vision of today's politicians is going to lead. He admires all four points of the Point 4 program, but he does not be-

lieve that the principles of world ecology can be reduced to four points. The ecologist keeps coming back to Puerto Rico, Ireland, England, Europe, India, China and Southeast Asia. He witnesses the surplus Puerto Ricans migrating to Harlem, and he watches the North Korean and Chinese casualty list pass the million mark. He reads in the newspapers that a new weapon burns up many soldiers at a single burst, and he learns that nerve gases, atomic weapons and biologic warfare may prove effective agents of destruction when the human weeds have grown too thickly. He wonders why peace and war are not subjected to exhaustive scientific inquiry as manifestations of community health and disease — like nonparalytic and paralytic poliomyelitis. He wonders why troubled Puerto Rico, historic Italy and peaceful Switzerland are not studied more intensively by WHO in order to determine not how to increase the numbers of inhabitants but how to improve the quality of their lives. Moreover, the ecologist believes, quite as profoundly as the public-health administrator believes in health, that it is necessary to determine how to maintain a balanced population within a given land area such as Puerto Rico or the state of Massachusetts before releasing the levers that control population equilibrium in all the "underdeveloped regions of the world."

References

1. President of World Health Assembly praises influence of WHO in raising health standards. Press Release of the Pan American Sanitary Bureau, Regional Office, World Health Organization, Washington, D. C., May 9, 1951.
2. Notestein, F. W. Needs of world population. *Bull. Atomic Scientists* 7:99, 1951.
3. Fitzgerald, D. A. World needs and resources. *Bull. Atomic Scientists* 7:102, 1951.
4. Sax, K. Food resources and population growth. *Bull. Atomic Scientists* 7:105, 1951.

THE ART OF MEDICINE

Manual dexterity in a variety of forms has always been associated with the art of medicine. This in no way refers to the once popular laying on of hands, which required no particular skill, but rather to an interest in the precise manipulation that is part of the stock in trade of the physician and surgeon as well as of the artisan and the artist.

Prior to the advent of relatively painless operative technics, surgeons found it particularly desirable to be nimble-fingered and took pains to develop both facility and speed in fulfilling the requirements of their professional procedures. Most of them had hobbies requiring manual skill. Many were violinists. Some made their own surgical instruments, carving elaborate designs on the bone handles. They developed incredible speed in operating; one surgeon is said to have amputated an arm during the time in which a spectator turned aside to take a pinch of snuff — and missed the show; another is credited with having removed a limb, three of his assistant's fingers and a bystander's coattails with a single sweep of his possibly homemade knife.

A well-known pediatrician who is also a most convincing magician and a lightning prestidigitator need not necessarily remind one of the *periodeuteis* or of those less honorable cutters for stone who sometimes skilfully palmed a spurious calculus to be used as Exhibit A after the operation. A contemporaneous surgeon may also be mentioned who made his office furniture while waiting for his first patients. His training as a surgeon was apparently dominant over his skill at cabinetmaking, there being no record extant of any difficulties that he might have encountered in shifting from a rabbeting plane to those instruments with which surgeons occasionally remove parts of the autonomic nervous system, for instance.

In this general category of accomplishments the recent exhibition of works of art by members of the Massachusetts Physicians Art Association, which took place during the annual meeting of the Massachusetts Medical Society, afforded a striking example of the ways in which the doctor has found solace in creative art. Less practical than cabinetmaking but equally useful as a distraction from the cares of professional life, the employment of brush and pen and modeling clay has found its place in the avocational life of the physician and has demonstrated a steady improvement in his technic and an increase in his imaginative perception from year to year.

It is only practical that this exhibition should be limited to bona fide works of art. The space and facilities required for a comprehensive doctor's hobby show might tax those of the Boston Garden,

even though such an exhibition would give convincing evidence of the variety of stars to which the sons of Aesculapius have hitched the painted wagons of their leisure hours.

MUMPS IMMUNIZATION

In 1934, Johnson and Goodpasture[1] established the etiology of mumps as a filtrable virus. Enders and Cohen[2] in 1942 confirmed their findings and extended them by developing a complement-fixation test that permitted the identification of this virus. Using this test for the detection of mumps virus, Habel,[3] at the National Institute of Health, and Levens and Enders,[4] at Harvard, almost simultaneously in 1945 succeeded in propagating this virus in the developing chick embryo. The stage was thus set for the development of improved methods for the diagnosis of mumps and its complications and for further extensive serologic and epidemiologic studies leading to the development of suitable preventive vaccines.

Numerous studies utilizing these new tools have since been reported from this country and elsewhere; these have been summarized by Enders[5] and by Gordon and Kilham.[6] Many of the serologic and epidemiologic observations with the mumps virus have been confirmed and extended in a carefully designed and executed series of studies recently reported by the Henles and their co-workers.[7-10]

The results of their studies of over 1800 skin tests and over 1500 complement-fixation tests[7] carried out with mumps virus that had been produced in embryonated hens' eggs showed a correlation with past known infections in the order of 70 to 80 per cent. Neither the positive complement fixation nor the positive skin test afforded absolute assurance of resistance to mumps. Nevertheless, the incidence of infections among persons with positive tests was below 2 per cent in 2 separate epidemic groups that were studied, as compared with about 19 per cent among those giving negative tests in one of these studies and 49 per cent in the other. Since there were some discrepancies between the results of the two kinds of tests, the authors believed that both the skin test and the complement-fixation test should be employed in determining the immune status of a subject.

The Philadelphia investigators also studied the effect of the intradermal injection of the mumps skin-test antigen on antibody formation and on immunity to mumps.[8] Not infrequently subjects who had negative serologic reactions prior to the skin test subsequently developed complement fixing and other antibodies. However, since adults demonstrated such an antibody response to the skin test more frequently and in higher titers than children under five years old, they believed that these responses represented in many instances a recall phenomenon (anamnestic reaction) and not de-novo antibody formation. This interpretation was strengthened by the failure to interrupt the course of mumps outbreaks in several institutions by application of skin tests. The incidence of mumps in skin-tested and control groups of children in these institutions was nearly identical.

The results of previous workers who showed that inactivated mumps virus injected subcutaneously in susceptible human beings will elicit antibodies was confirmed, as was also the observation that the antibodies so produced are indicative of protection against infection.[9] The immunity thus produced was transitory, its duration being related to the height of the antibody level attained. Large quantities of virus were found necessary to assure protection against mumps. The amount required to produce measurable antibodies in nearly all susceptible persons was about 4 cc. of concentrated vaccine, representing about 80 cc. of infected allantoic fluid, or the harvest from more than ten chick embryos. The use of such vaccines in this manner on a large scale would thus seem to be almost prohibitively expensive.[10]

Enders and his co-workers[11] in 1946 showed that the mumps virus after 25 egg passages was no longer capable of inducing mumps in monkeys and in presumptively susceptible human beings when sprayed into the oral cavity. Nevertheless, by this procedure the monkeys were rendered immune to subsequent inoculation of virulent virus and antibodies were produced in the human beings. Pursuing these leads, the Henles and their collaborators[10] studied the response of 410 presumptively

susceptible children to oral spraying of attentuated active mumps virus produced in eggs. Only 6 developed mild infection and up to 93 per cent developed antibodies in some groups, depending on the concentration of virus used. In most instances the serologic tests were negative one year after the spraying, but after skin tests at that time the antibody response was greater in these children than in comparable control subjects. Experimental exposure of 4 children to mumps virus three months after immunization failed to elicit the disease, whereas 4 out of 6 controls developed clinical evidence of mumps after similar exposure. There was also suggestive evidence of protection during an institutional outbreak eight months after oral vaccination.

These and other studies by different groups of workers offer the prospect of successful application of large-scale immunization against mumps in the near future.

References

1. Johnson, C. D., and Goodpasture, E. W. Investigation of etiology of mumps. *J. Exper. Med.* **59**: 1-19, 1934.
2. Enders, J. F., and Cohen, S. Detection of antibody by complement-fixation in sera of man and monkey convalescent from mumps. *Proc. Soc. Exper. Biol. & Med.* **50**:180-184, 1942.
3. Habel, K. Cultivation of mumps virus in developing chick embryo and application to studies of immunity to mumps in man. *Pub. Health Rep.* **60**:201-212, 1945.
4. Levens, J. H., and Enders, J. F. Hemoagglutinative properties of amniotic fluid from embryonated eggs infected with mumps virus. *Science* **102**:117-120, 1945.
5. Enders, J. F. Virus as antigen with special reference to mumps. *The Harvey Lectures*, Series XLIII, 1947-1948. Springfield, Illinois: Charles C Thomas, 1950. Pp. 92-120.
6. Gordon, J. E., and Kilham, L. Ten years in epidemiology of mumps. *Am. J. M. Sc.* **218**:338-359, 1949.
7. Henle, G., Henle, W., Burgoon, J. S., Bashe, W. J., Jr., and Stokes, J., Jr. Studies on prevention of mumps. I. Determination of susceptibility. *J. Immunol.* **66**:535-549, 1951.
8. Henle, G., et al. Studies on prevention of mumps. II. Effect of skin testing upon antibody level and resistance. *J. Immunol.* **66**:551-560, 1951.
9. Henle, G., et al. Studies on prevention of mumps. III. Effect of subcutaneous injection of inactivated mumps virus vaccines. *J. Immunol.* **66**:561-577, 1951.
10. Henle, G., et al. Studies on prevention of mumps. IV. Effect of oral spraying of attenuated active virus. *J. Immunol.* **66**:579-594, 1951.
11. Enders, J. R., et al. Attenuation of virulence with retention of antigenicity of mumps virus after passage in embryonated egg. *J. Immunol.* **54**:283-291, 1946.

WITHOUT SCRUPLES

THE word *fractious*, meaning, according to no less eminent an authority than Webster (Noah, not Daniel), "apt to break out into a passion. . . peevish, waspish, irritable, perverse," is derived no doubt from the same Latin root as is *fraction*. And many a temper and many an ambitious young elementary scholar's aspirations have been fractured against the arithmetical obstacles presented by the fraction.

A simple way out of these mathematical difficulties, however, was invented by certain logical minds in the form of the decimal system. With the help of this device and by sheer weight of numbers the fragments of the pointless numerator-and-denominator method of calculation can be removed from the picture.

Old customs die hard; although this country enthusiastically adopted at the very beginning a decimal coinage and, some believe, has continued the adoration of it ever since, the pound, the pint and the inch are still fixed institutions, and only in comparatively recent years have the gram and the milliliter begun to prevail over the scruple, the minim and the grain.

This being the case in a land whose traditions are either relatively new or transplanted, it is with an element of surprise that the somewhat tardy follower of current events learns of certain developments that have been transpiring in Great Britain.

The Committee on Weights and Measures Legislation of the Board of Trade, according to a leading article in the *British Medical Journal* of May 26, 1951, has recommended that weights and measures in medicine and pharmacy should be given entirely in the metric system. Eventually, in fact, the committee would like to see the entire imperial system replaced by the metric, and even advocates a decimal coinage.

Medicine in Great Britain is at present functioning in a bivalent manner, with so many of the newer chemical products listed in doses measured by the metric system. A beneficent five-year program, if sturdily adhered to, should, in the opinion of the committee, effect the transition, so far as medicine and pharmacy are concerned. But when pounds and pence are abandoned in favor of dollars and cents, Old England will certainly be in the way of becoming another New England.

An old woman in Salem, 76 years of age, is bedecked with a new crop of chestnut hair. These efforts of nature at a renewal of any part of the system, often seem to induce immediate organic derangement, and life is shortened by it.

Boston M. & S. J., *July 9, 1851*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

HYDE — Harold V. Hyde, M.D., of Cambridge, died on June 20. He was in his sixty-fourth year.

Dr. Hyde received his degree from Harvard Medical School in 1914. For many years he served on the staff of the Boston City Hospital and was visiting surgeon at the Mount Auburn Hospital, Cambridge. He was a fellow of the American College of Surgeons.

A daughter survives.

LITTLEFIELD — George C. Littlefield, M.D., of Webster, died on June 14. He was in his seventy-ninth year.

Dr. Littlefield received his degree from Bowdoin Medical School in 1897. He was a fellow of the American Medical Association.

There are no immediate survivors.

MISCELLANY

BERTNER FOUNDATION AWARD

The second annual award of the Bertner Foundation has been conferred on Dr. Fred W. Stewart, pathologist for the Memorial Hospital Center for Cancer and Allied Diseases, New York City.

On April 21 Dr. Stewart delivered the Bertner Lecture at the University of Texas M. D. Anderson Hospital's Fifth Annual Symposium on Fundamental Cancer Research in Houston.

CORRESPONDENCE

ARE LECTURES ENOUGH?

To the Editor: I wish to commend the recommendation of the Committee on Membership of the Massachusetts Medical Society to the Executive Committee in regard to postgraduate study lecture courses for graduates of formerly unapproved or foreign medical schools.

It is noteworthy that, unapproved schools having ceased to exist, the American Medical Association has recommended to recognized hospitals the admission of these graduates as interns and residents; as a corollary, they should be admitted to at least the courtesy or community-hospital staff.

Since the gates of most hospitals have been closed to graduates of unapproved schools, an unhealthy practical and educational problem has arisen; one cannot deny doctors the benefits of modern hospital guidance, training and education and expect the competent physicians or beneficial advantages to the patient that result from improved medical knowledge, technical skill and the advantages of improved hospital facilities and well trained staffs.

Some hospitals are now imposing further residency and long waiting periods; hospital admissions having increased, instead of more or larger hospitals, admissions are restricted to emergencies or to cases of the higher-ranking staff members; public institutions have become restricted to the use of a few persons. This is an unhealthy and explosive situation for both the physician and his patients, forcing the patients to seek government aid for more hospitals or government medical care and forcing the doctor to enter specialized practice or small, inferior or nondescript hospitals that offer none of the known advantages.

Well-educated physicians can come only from a good hospital that supervises, trains and stimulates interest in reading or postgraduate studies. One learns by doing, for which there is no substitute.

Norman S. Goetz, president of the Hospital Council of Greater New York, states: "The level of practice within any community depends primarily upon the association of its physicians with hospitals. The addition of more physicians to the staffs of hospitals with the resultant opportunities for their education, training and guidance is to be regarded as a call upon the conscience of our hospital governing boards. Many of the physicians who do not have opportunities are general practitioners."

The graduates of unapproved schools are in an even worse plight, because of misinformation, prejudice and remaining hospital restrictions imposed by the American Medical Association in its effort to have only qualified medical schools.

The Committee on Hospital and Professional Relations and the Executive Committee of the Council should make a concerted effort to open up hospital facilities on a more equitable basis or, as recommended by Dr. H. Quimby Gallupe, for the postgraduate hospital training and education of physicians from unapproved schools.

Similarly, Dr. Gallupe, in a message to Middlesex West District Society, advocated admission to hospital privileges of every registered physician in the community.

ALEXANDER YOUNG, M.D.

Hull, Massachusetts

BOOK REVIEW

Medical Books, Libraries and Collectors: A study of bibliography and the book trade in relation to the medical sciences. By John L. Thornton, A.L.A., librarian, St. Bartholomew's Hospital Medical College. With an introduction by Geoffrey L. Keynes, M.A., M.D., F.R.C.S. 8°, cloth, 293 pp., with 19 illustrations. London: Grafton and Company, 1949.

Mr. Thornton has accomplished in his book a pleasing and instructive blending of the history of medicine, the making and distribution of books, the listing of material and the preservation and servicing of the written and printed word in medical libraries designed for that purpose.

Before the invention of printing, either from wood blocks or from metal type, the medium of expression, except for spoken language, was limited to various types of manuscripts. The author begins his story with this period and carries it through the centuries to the nineteenth.

Fifteenth-century books have benefited by the strongest concentrated study to the present time. It must be remembered that a perspective of a few hundred years is required for a true evaluation of any period.

Neuberger, in writing his great history of medicine, found it too difficult to continue his work beyond the early period. Likewise, Sarton, in his monumental work on the history of science, has only reached the thirteenth century. What is needed urgently at the present time is a listing of the sixteenth-century writings and an evaluation of the knowledge of that century.

Thornton's book is a mine of information about the history of medical societies, periodical literature, medical bibliography and bibliographers, medical publishing and bookselling and medical libraries, public and private. The two appendixes are invaluable, providing chronologic lists of medical societies and institutions and of medical libraries and institutions that have large medical collections.

There is a good index, and the book is well published. The reviewer has found it necessary to read almost every word of the text, and finds that the author is unprejudiced and gives credit where credit is due. The book is recommended for all medical and public libraries, and should be on the desk of every medical librarian and historian.

JAMES F. BALLARD

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Post-Graduate Lectures on Orthopedic Diagnosis and Indications. By Arthur Steindler, M.D., professor of orthopedic surgery, State University of Iowa College of Medicine. Vol. 1. 4°, cloth, 280 pp., with 290 illustrations. Springfield, Illinois: Charles C Thomas, 1950. $7.50.

In these lectures Dr. Steindler has summarized his extensive knowledge of the subject gained from thirty years' experience in practice. The lectures are divided into two parts: propedeutics in orthopedic diagnosis; and congenital deformities and disabilities. The first part discusses symmetry and asymmetry of the body, contractures, interpretation of pain in orthopedic surgery and the pathology of gait. The second

treats of congenital deformities and disabilities in general and conditions due to disturbance of bone growth: the chondrodystrophies, congenital deformities of the spine and thorax, congenital talipes, congenital defects and malformations of the long bones of the extremities, congenital dislocation of the hip and congenital deformities of the upper extremities. The book is well published, and there are indexes of subjects and authors. The volume should be in all collections on orthopedics.

The Esophagus and Pharynx in Action: A study of structure in relation to function. By William Lerche, M.D., 8°, cloth, 222 pp., with 93 illustrations. Springfield, Illinois: Charles C Thomas, 1950. $5.50.

In this monograph the author discusses the closing mechanism between the stomach and the esophagus on the basis of his experimental researches and a survey of the literature on the subject. A bibliography of 226 references is appended to the text, and there are indexes of subjects and authors. The monograph should be in all collections of physiology and gastroenterology.

Clinical Examination of Patients: With Notes on Laboratory Diagnosis. By John Forbes, M.D., M.R.C.P., physician to the Wrexham Hospitals, and W. N. Mann, M.D., F.R.C.P., assistant physician to Guy's Hospital. 8°, cloth, 323 pp., with 60 illustrations. Baltimore: Williams and Wilkins Company, 1950. $4.50.

This small volume is intended as a guide to the student during his introduction to clinical medicine. The text is well illustrated, there is a good index, and the publishing is excellent. The printing was done in Great Britain.

The Antihistamines: Their clinical application. By Samuel M. Feinberg, M.D., associate professor of medicine, chief, Division of Allergy, and director, Allergy Research Laboratory, Northwestern University Medical School; Saul Malkiel, Ph.D., M.D., assistant professor of medicine and director of research, Allergy Research Laboratory, Northwestern University Medical School; and Alan R. Feinberg, M.D., clinical assistant in medicine and attending physician in Allergy Clinic, Northwestern University Medical School. 12°, cloth, 291 pp., with 26 illustrations. Chicago: Year Book Publishers, Incorporated, 1950. $4.00.

The text of this small monograph is divided into two parts: experimental studies on histamine and the antihistamines; and clinical observations, discussing respiratory allergy, dermatoses, miscellaneous allergic manifestations, administration and dosage, and toxic effects of the antihistamines. There is an extensive bibliography of 586 references and a good index. The monograph should be in all collections on allergy.

Cerebral Palsy. By John F. Pohl, M.D., orthopedic surgeon, Michael Dowling School for Crippled Children, Minneapolis, Minnesota. 8°, cloth, 224 pp., with 131 illustrations. Saint Paul, Minnesota: Bruce Publishing Company, 1950. $5.00.

This small book is devoted to treatment and especially to neuromuscular training. There is a good index. The book is well published and should be in all collections on the subject.

Pneumoconiosis: Beryllium, bauxite fumes, compensation. (Leroy U. Gardner Memorial Volume.) Edited by Arthur J. Vorwald, M.D., director, Trudeau Foundation and Saranac Laboratory. With the collaboration of Manfred Bowditch, A. B., Thomas M. Durkan, M.E., and Theodore C. Waters, L.L.B. 8°, cloth, 659 pp., with 196 illustrations and 78 tables. New York: Paul B. Hoeber, Incorporated, 1950. $7.50. (Sixth Saranac Symposium.)

This composite volume comprises 39 articles by different authors on the various aspects of the beryllium problem. They constitute the papers read at the sixth Saranac symposium. The material is divided into seven parts: history and industrial aspects; the acute disease; the chronic or delayed disease; toxicity studies in connection with atomic-energy production; experimental aspects; Shaver's disease; and compensation for occupational disease. A bibliography of forty-eight pages concludes the text. There is a good index, and the book is well published. This treatise should be in all collections on occupational diseases and toxicology.

Bibliographia Medica Helvetica. Vol. VI (1948). 8°, paper, 541 pp. Basel: Benno Schwabe and Company, 1950. Broschiert Fr. 15 — (Distributed by Grune and Stratton, New York.)

This sixth volume of a medical bibliography of Swiss writings is well published. It has comprehensive indexes of authors and subjects. The price is reasonable, and the volume should be in all collections of medical bibliography.

O Que o Diabético Deve Saber. By Dr. Francisco Arduino, assistente da 5. Cadeira de Clinica Médico de Faculdade Nacional de Médicina, medico da Assistência Municipal. Apresentãcao do Prof. Luiz A. Capriglione. 8°, paper, 100 pp., with 15 illustrations. Rio de Janeiro: Grafica Santa Cecilia, 1950.

This popular manual for the diabetic patient discusses the various aspects of diabetes and its treatment and control.

A Text-Book of Venereal Diseases. By R. R. Willcox, consultant in venereal diseases, St. Mary's Hospital, London, physician-in-charge, Venereal Diseases Department, King Edward VII Hospital, Windsor (N. W. Metropolitan Regional Hospitals Board), and member, Council Society for Study of Venereal Diseases, London. 8°, cloth, 439 pp., with 154 illustrations. New York: Grune and Stratton, 1950. $5.00.

This new book on the venereal diseases is divided into three parts: gonorrhea, syphilis and the various agents of treatment. The text is well written, there is a good index, and the publishing is excellent. The printing was done in Great Britain.

Significance of the Body Fluids in Clinical Medicine. By L. H. Newburgh, M.D., professor of clinical investigation, University of Michigan Medical School, assisted by Alexander Leaf, M.D., instructor in internal medicine, University of Michigan Medical School. 8°, cloth, 76 pp., with 16 illustrations and 6 tables. Springfield, Illinois: Charles C Thomas, 1950. $2.00.

This small monograph is based on the Ernest A. Sommer Memorial Lectures delivered at Portland, Oregon, in 1946. The text is divided into two parts: physiology and clinical significance.

Leitfaden für Prostatiker. By Professor Dr. med. J. Minder, Spezialarzt der Urologie in Zürich. 8°, paper, 68 pp., with 7 illustrations. Stuttgart: Georg Thieme, 1950. Kartoniert DM 4.80.

This small manual discusses all the aspects of prostatic disease. *Die Lunge des Kindes: Wachstum, Anatomie, Physiologie und Pathologie in den verschiedenen Altersperioden.* By Professor Dr. Stefan Engel, London. 8°, cloth, 288 pp., with 283 illustrations. Stuttgart: Georg Thieme, 1950. Ganzleinen DM 29.70.

This book is a German translation of the English edition. The text is divided into two parts: the bronchial tree and glands; and the lung. The author discusses the growth, anatomy, physiology and pathology of the bronchus and lung in various age periods of children.

Carbon Dioxide Therapy: A neurophysiological treatment of nervous disorders. By L. J. Meduna, M.D., professor of psychiatry, University of Illinois College of Medicine. 8°, cloth, 236 pp., with 9 illustrations. Springfield, Illinois: Charles C Thomas. 1950. $5.00.

This monograph presents the investigations of the author on a special treatment of the psychoneuroses. The text is divided into a number of parts on the central actions of carbon dioxide, its effect upon the function of isolated nerve and upon the function of the brain, technic and administration in treatment, and material and statistical data. A final chapter presents a neurophysiologic theory of psychoneuroses. A bibliography is appended to the text. The monograph should be in all collections on psychiatry and neurology.

(*Notices on page xiii*)

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SOCIETY MEETINGS AND CONFERENCES

SEPTEMBER 4–8. American Congress of Physical Medicine. Page 238, issue of February 8.

SEPTEMBER 12–14. Biological Photographic Association, Inc. Annual Meeting, Boston.

SEPTEMBER 19. American Medical Writers' Association. Page 1066, issue of December 28.

SEPTEMBER 19-21. Mississippi Valley Medical Society. Page 1066, issue of December 28.

SEPTEMBER 30–OCTOBER 2. New Hampshire Medical Society. Annual Meeting. Equinox House, Manchester, Vermont.

OCTOBER 29. New York Institute of Clinical Oral Pathology. Page xv, issue of June 14.

OCTOBER 31. New England Obstetrical and Gynecological Society. Hotel Somerset, Boston.

NOVEMBER 7–19. Pan-Pacific Surgical Association. Page 820, issue of May 24.

DECEMBER 14 AND 15. Association for Research in Nervous and Mental Disease. Page 958, issue of June 21.

JULY 8–11, 1952. Thirteenth British Congress of Obstetrics and Gynaecology. Page xv, issue of December 14.

JULY 14–19, 1952. International Congress of Physical Medicine. Page 998, issue of June 28.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JULY 12

THURSDAY, JULY 12

*9:00–10:00 a.m. Grand rounds. Robert Breck Brigham Hospital.

FRIDAY, JULY 13

*9:00 a.m.–12:00 m. Combined medical and surgical staff rounds. Peter Bent Brigham Hospital.

*10:00 a.m. Surgical clinic. South End Health Unit, 57 East Concord Street, Boston.

12:00 m.–1:00 p.m. Clinicopathological Conference (Boston Floating Hospital). Joseph H. Pratt Diagnostic Hospital.

*1:30 p.m. Tumor clinic. Outpatient Department, Mount Auburn Hospital, Cambridge.

MONDAY, JULY 16

*11:30 a.m.–12:15 p.m. Clinical conference. South End Health Unit, 57 East Concord Street, Boston. Dr. Cleaveland Floyd in charge.

*12:15–1:15 p.m. Clinicopathological conference. Main Amphitheatre, Peter Bent Brigham Hospital.

TUESDAY, JULY 17

*12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.

*1:30–2:30 p.m. Pediatric rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

*Open to the medical profession.

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